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# The Journal of Laboratory and Clinical Medicine

VOL. III. ST. LOUIS, JUNE, 1918 No. 9


## ORIGINAL ARTICLES

### RESEARCHES IN RHEUMATISM*


BY WILLIAM LINTZ, M.D., BROOKLYN, N. Y.


ANY work which will shed some light as to the etiology of rheumatism is very desirable since our knowledge as to the definite cause of this widespread disease is still in darkness. With this object in view I have investigated the blood of a great many cases of rheumatism, particularly of the acute articular type, but in only four cases was I successful in isolating microorganisms in the blood. Why the percentage of positive findings is so small is as yet not clear to me, unless the bacteria are lodged within Aschoff's nodes as I have described previously.†

The object of this work is

1. To demonstrate that in at least a small percentage of cases of acute articular rheumatism a definite microorganism can be isolated from the blood.

2. To describe in detail the study of the bacteriology and biochemistry of the bacteria isolated.

3. By animal experimentation to establish the pathogenicity of the microorganism, and its relationship to rheumatism isolated.

Let us consider these in the order mentioned.

1. A brief summary as to the different views elaborated to explain the causes of rheumatism is but fair in order to bring out all the phases of this important question.

A. Rheumatism was attributed by Cullen to be caused by cold acting directly upon the joints thus setting up a local inflammation, which is followed by a general fever. Exposure thus causing an irritation of the cutaneous sensory nerve fibers would set up a central disturbance in the cord and medulla oblongata.


*From Hoagland Laboratory of Long Island College Hospital, Brooklyn, N. Y.


†Rheumatic Carditis, Jour. Am. Med. Assn., March 2, 1912.

This disturbance was transmitted to the nerves of the various organs which were involved by acute rheumatism and caused in turn the various manifestations of the disease.

B. Chemical theory: Both uric and lactic acids are supposed to be the cause, for they have been demonstrated in excess in patients suffering from rheumatism.

C. Infectious theory: This is viewed from various angles.

(1) Some believe there is no specific bacteria, but that the disease is a form of septicemia caused by staphylococcal or streptococcal infection.

(2) Some, that the disease is due to a specific bacillus (Achalme, 1891).

(3) Some, that the microorganism is a specific diplococcus. (Discovered by Triboulet in 1897.)

(4) That the microorganism has as yet not been discovered.

It seems to me that the first view (A) hardly needs to be considered, for it is entirely dispelled by the light shed by modern pathology. Such a pathogenesis would be indeed unique. The second view (B) hardly deserves more serious attention. For it is one thing to demonstrate an excessive formation of such substances, and another to prove them the cause and not the result of the disease. Besides, what one chemical substance will satisfactorily account for all the phenomena of rheumatism?

There is no doubt that the disease is caused by a microorganism, for the following reasons:

Sometimes this disease occurs in epidemics, as described by Strümpell in Leipzig, by Large in Copenhagen, and several have been observed in London.

The disease is self limited.

The severer symptoms and complications suggest those of other infections, some like pyemia, gonorrhea, scarlatina, typhoid fever, and cerebrospinal meningitis, may present joint symptoms.

All the experimental evidences by numerous workers go to the support of the bacterial cause of the disease. To me the report of James M. Beattie* is very significant towards proving the infectiousness of rheumatism. He reports four cases of typical subacute articular rheumatism of long standing which presented amyloid degeneration of the organs. There was no other condition clinical or pathologic to account for this amyloid degeneration except rheumatism. Though it is true that the cause of amyloid degeneration is not clearly understood, yet it is generally regarded that it is secondary to some infectious agent, and that most generally bacterial in nature.

2. The four cases which yielded positive blood cultures were typical cases of acute articular rheumatism. Here the correct diagnosis is of the utmost importance. I will therefore cite the history of one of these cases, the other three cases presented practically the same symptoms and ran the same course. To cite them in detail would be merely a question of repetition.

Case P. L., Hospital No. 4644, was admitted to the Brooklyn Jewish Hospital on Jan. 1, 1910. His family history, as well as previous and venereal histories were negative, and had no bearing upon the present illness. His habits were good. His present illness began

*Jour. Exper. Med., March 4, 1907.

about a week before admission to the hospital with fever and sweating and pains in knees. The course of the disease which the patient ran under our very eyes, and the symptoms which he presented, were typical of that of acute articular rheumatism. The inflammation spread from joint to joint until all of the larger joints of the body were involved, some of the joints improving, while fresh ones became affected. The joints were swollen, red and hot and exquisitely tender. The patient suffered from excruciating pains in the limbs and particularly in the joints. At times he was rather restless and delirious and perspired profusely. The patient felt exceedingly weak. While in the hospital he developed a blowing systolic murmur at the apex which was transmitted to the left and posteriorly. His left border of the heart was slightly enlarged. All other examinations of his thoracic and abdominal viscera were negative. His tonsils were moderately enlarged and congested. His temperature ranged from 100° to 104°, pulse from 80 to 125, and respirations from 20 to 40. His urine examinations showed albumin granular and hyaline casts and crystals of phosphates, oxalates, and at times urates. Otherwise it was negative.

*Blood Examinations.*—Reds 5,000,000, Hb. 60 per cent. White blood cells varied from 11,000 to 18,000, polymorphonuclears went as high as 84 per cent, and lymphocytes varied from 16 to 32 per cent. Blood pressure varied from 112 to 130.

The treatment consisted in the administration of moderate doses of alkalies and aspirin, and the local application to the joints of oil of wintergreen. He made an uneventful but complete recovery, leaving him no stiffness of limbs, and the heart sounds became normal. The patient was discharged cured on Feb. 27, 1910.

On the sixteenth day, at the height of the disease, a positive blood culture was obtained. This was repeated Jan. 23, the twenty-third day of the disease, and the same microorganism was isolated. There were only 4 to 5 bacteria per cubic centimeter of blood. The method employed in the blood culture is that of Castellani and Schöttmuller; i. e., both fluid and solid media were employed to plant the blood, 10 to 20 c.c. of blood being employed for this purpose.

That the above case was one of typical acute articular rheumatism, no one will doubt. That the microorganism isolated actually came from the blood and was not a contamination, we must accept, since the same microorganism was isolated upon a repeated blood culture, and upon all of the various media.

What has been said of the above case is practically true of the remaining cases. To cite them in detail would be merely a question of repetition. All were typical cases of acute articular rheumatism. At the height of the disease a positive culture was isolated from the blood. The blood culture was repeated a few days later and the same microorganism isolated. The microorganism isolated was a gram-positive diplococcus with a tendency towards the formation of short chains.

## BACTERIOLOGIC INVESTIGATIONS

The question naturally arose, "Is this microorganism isolated a specific germ, or is it one of the many forms of streptococci?" To determine this the

TABLE I

| | | A | B | C | D | X | Y | Z |
|---|---|---|---|---|---|---|---|---|
| 1 | FORM | COCCUS | COCCUS | COCCUS | COCCUS | COCCUS | COCCUS | COCCUS |
| 2 | SIZE | 1 μ | 1 μ | ¾ μ | 1 μ | 2 μ | 2 μ | 2 μ |
| 3 | ARRANGEMENT | mainly in pairs | short chains | pairs and short chains | mainly in pairs | long chains | short chains | moderate chains |
| 4 | GRAM STAIN | positive | positive | positive | positive | positive | positive | positive |
| 5 | CAPSULES | none | none | none | none | none | none | none |
| 6 | MOTILITY | none | none | none | none | none | none | none |
| 7 | GRANULES | none | none | none | none | none | none | none |
| 8 | SPORES | none | none | none | none | none | none | none |
| 9 | FLAGELLAE | none | none | none | none | none | none | none |

TABLE II

AEROBIC GROWTHS, 24-HOUR CULTURES AT 37.5° C.

| | | A | B | C | D |
|---|---|---|---|---|---|
| I | AGAR | Very profuse growth, colonies extremely minute, almost microscopic, grayish white in appearance, round edges, homogeneous, slightly raised, discrete although occasionally confluent. Edge of growth granular in appearance due to discrete colonies. Water of condensation clear. No change in media. 48 hr. growth—no change.<br>*Microscopic*—Gram-positive diplococci. | Same as A.<br>Gram-positive diplococci | Growth moderate, glistening, colonies are raised, round, convex, 1/10 to 1/4 mm. in diameter, media is unchanged, and water of condensation is perfectly clear. | Same as C, except that there is a slight granular precipitate in liquor condensation. |
| II | GLUCOSE AGAR (SLANT) | Growth more profuse, colonies more confluent, somewhat larger, pin point.<br>Otherwise same as above. Heavy growth in water of condensation.<br>48 hour growth—more profuse, cloudiness and uniform precipitation of media.<br>*Microscopic*—Gram-positive diplococcus, 1 micron in diameter. | Same as A.<br>48 hr. growth, slight cloudiness of media.<br>Same. | Growth moderate, otherwise same as above.<br>Growth unchanged after 72 hr. | Growth opaque, abundant, glistening; colonies round, convex 1/10 to 1/4 mm. in diameter. Liquor condensation turbid, with marked granular sediment. |
| III | GLUCOSE AGAR (STAB) | Profuse growth limited to needle track, no branching out into media.<br>Growth homogeneous throughout, i. e., lower half just as thick as upper half. No gas formation. Colonies same as on I.<br>48 hr. growth uniform, cloudiness, and precipitation of media; no gas formation.<br>*Microscopic*—Gram-positive diplococci, 1 micron in diameter. | Same as A.<br>48 hr. slight cloudiness of media.<br>Same. | Slight growth along stab for 1/8" from surface, grayish white in appearance.<br>72 hr. no change, growth scanty, and limited to needle track. No gas formation. | Same as C. |
| IV | SERUM AGAR | Very profuse growth having same characteristics as I. No liquefaction of media. Heavy growth in water of condensation.<br>48 hr. growth more profuse.<br>*Microscopic*—Gram-positive diplococci and short chains. | Same as A.<br>48 hr. same as A. | Grayish white discrete colonies, round, elevated, size of "period dot."<br>Growth moderate, heavy growth in water of condensation. No liquefaction of media.<br>72 hr growth more abundant, otherwise unchanged. | Same as C. |
| V | GLUCOSE SERUM AGAR | Extremely profuse growth. Marked clouding and precipitation of media. Surface granular. Colonies white or milky gray, round and size of "period." Thick and flocculent growth in water of condensation. No gas formation. There is marked precipitation of media giving it a milky color. No liquefaction of media.<br>48 hr. growth more profuse and more precipitation of media (This is optimum media.)<br>*Microscopic*—Gram-positive diplococci and short chains. | Same as A.<br>48 hr. same as A. | Moderate growth same as IV.<br>72 hr. growth same as IV. No precipitation of media. growth scanty. Few discrete opaque colonies. | Same as C. |
| VI | GLYCERIN AGAR | Growth sparse, hardly perceptible with naked eye, colorless and translucent. Colonies are microscopic, discrete. No cloudiness of water of condensation.<br>48 hr. meager growth, colonies microscopic.<br>Gram-positive diplococci and short chains. | Growth somewhat more profuse, otherwise same as A.<br>48 hr. growth—no change.<br>Same. | No growth.<br>48 hr. no growth.<br>Same. | No growth.<br>48 hr. growth no change.<br>Same. |

TABLE II—CONT'D

AEROBIC GROWTHS, 24-HOUR CULTURES AT 37.5° C.

| | | A | B | C | D |
|---|---|---|---|---|---|
| VII | GLYCERIN SERUM AGAR | Growth very sparse, almost imperceptible. Few microscopic translucent colonies. Water of condensation clear and no liquefaction of media.<br>48 hr. fairly profuse growth of microscopic, translucent, discrete and confluent colonies. Growth in water of condensation.<br>Gram-positive diplococci and short chains. | No growth.<br>48 hr. no growth.<br>Same. | No growth.<br>72 hr. no growth.<br>Same. | No growth.<br>48 hr. No growth.<br>Same. |
| VIII | INULIN | No change, media not fermented.<br>48 hr.—no change.<br>*Microscopic*—Diplococci. | No change—no fermentation.<br>48 hr. no change.<br>Diplococci. | Fermentation present.<br>Diplococci. | Slight fermentation.<br>Diplococci. |
| IX | LITMUS MILK | Acid, no coagulation, white precipitate at bottom.<br>48 hr. acid, coagulated (test tube can be inverted without spilling contents).<br>*Microscopic*—Gram-positive diplococci and short chains. | Marked acid reaction Coagulation (contents solid). Moderate ppt. at bottom.<br>48 hr. white, and culture solid.<br>Same. | Marked acidity. Coagulation.<br>72 hr. solidification complete.<br>Same. | Same as C.<br>Same. |
| X | DUNHAM'S PEPTONE | Clear, no growth present.<br>48 hr. slight cloudiness and precipitate at bottom.<br>*Microscopic*—No bacteria. | Clear above and ppt. at bottom.<br>48 hr. diffuse slight cloudiness.<br>Chains of 2 and 4, few organisms present. | Same as B. | Same as B. |
| XI | ASCITIC SERUM | No change. No cloudiness.<br>48 hr. no change.<br>*Microscopic*—Short chains of cocci, some swollen, irregular and bacillary in shape. Degeneration form. | Distinct homogeneous moderate cloudiness; no granules and no ppt. at bottom.<br>48 hr. same as above.<br>*Microscopic*—Profuse short chains. | Same as B. | Same as B. |
| XII | PLAIN BOUILLON | Uniform cloudiness, no ppt.<br>48 hr. same.<br>*Microscopic*—Pairs and short chains. | Slight cloudiness.<br>48 hr. same.<br>Same. | Same as A. | Same as A. |
| XIII | GLUCOSE BOUILLON | Moderate uniform cloudiness of media, due to suspension of fine granules, which are grayish white in color varying in size from minute pin points to "period dots." Heavy grayish white granular ppt. at bottom.<br>48 hr. growth more profuse.<br>*Microscopic*—Pairs and short chains and in clumps resembling staphylococcus. | Same as A.<br>48 hr. same as A.<br>Very long and tortuous chains of cocci. | Same as A.<br>Mainly as diplococci. | Same as A.<br>Short chains. |
| XIV | BLOOD SERUM AGAR | Very profuse growth, edges of growth rough, due to discrete colonies. Colonies minute pin points, round and slightly elevated. *No hemolysis*, no liquefaction of media.<br>48 hr. growth more profuse, no hemolysis present.<br>Gram-positive diplococci and short chains. | Same as A.<br>Same as A.<br>Same. | Profuse growth, pin-point colonies. Slight hemolysis. Otherwise same as A and B.<br>Same. | Same as A.<br>Same. |

TABLE II—CONT'D

AEROBIC GROWTHS, 24-HOUR CULTURES AT 37.5° C.

| | | A | B | C | D |
|---|---|---|---|---|---|
| XV | GELATINE AT ROOM TEMP. 75° F. | Profuse growth only along stab. Colonies are very small and grayish white. No liquefaction of media.<br>48 hr. more profuse growth and beginning liquefaction.<br>*Microscopic*—Gram-positive diplococci. | Same as A.<br>Same as A.<br>Same. | Very fine growth. No liquefaction.<br>48 hr. same.<br>Same. | Same as C.<br>Same. |
| XVI | POTATO | Moderate colorless or slightly grayish growth. No change in media. No odor.<br>*Microscopic*—Short chains. | Same. | No growth. | No growth. |
| XVII | MANNIT 1% | Very profuse growth throughout media; no gas formation; no sediment.<br>*Microscopic*—Diplococci and few short chains. | Same but more sediment.<br>Moderately long chains. | Diffuse granular turbidity. No fermentation.<br>Diplococci. | Slight turbidity. No fermentation.<br>Diplococci. |
| XVIII | LACTOSE 1% | Very profuse growth. Heavy grayish white sediment. No gas formation. Growth thick and heavy near open end of fermentation tube, closed end almost clear.<br>*Microscopic*—Diplococci. | Same.<br>Diplococci. | Slight turbidity. No fermentation.<br>Diplococci. | Diffuse granular turbidity. No fermentation.<br>Diplococci. |
| XIX | LEVULOSE 1% | Profuse growth more heavy near open part of fermentation tube. Profuse grayish white granular sediment. No gas formation.<br>*Microscopic*—Mostly in clumps, here and there in diplococci and short chains. | Same.<br>Same. | Same. | Same. |
| XX | SACCHAROSE 1% | Very profuse growth same as XIX.<br>*Microscopic*—Gram-positive diplococci and short chains. | Same. No gas. Cloudiness of media more uniform.<br>Same. | Uniform turbidity.<br>Same. | Slight uniform turbidity.<br>Cocci microscopically. |
| XXI | SACCHARIN ½% | Very profuse growth and uniform cloudiness of media. No sediment (same as XVI). No fermentation.<br>*Microscopic*—Mostly in clumps; few diplococci. | Same. | Same. | Same. |
| XXII | SALICIN ½% | Diffuse uniform cloudiness. Slight grayish white sediment. No fermentation.<br>*Microscopic*—Mostly in clumps and diplococci. | Same.<br>Long chains. | Same as A. | Same as A. |
| XXIII | RAFFINOSE | Slight turbidity. No fermentation. No fermentation.<br>*Microscopic*—Gram-positive diplococci and few short chains. | Slight turbidity, no fermentation.<br>Same. | Slight granular turbidity. No fermentation.<br>Diplococci. | Slight turbidity. No fermentation.<br>Diplococci. |
| XXIV | MCCONKY (BILE SALTS) | Growth slight convex and glistening. Media salts apparently precipitated out. Colonies round, entire, convex, about ¼ mm. in diameter. Takes at least 2 to 3 days before growth appears.<br>*Microscopic*—Gram-positive diplococci, some in short chains. | Same as A.<br>Same. | Same as A.<br>Gram-positive diplococci and involution forms present. | Same as A. |
| XXV | BLOOD AGAR PLATES | Browned. Growth very abundant, discrete, glistening. Colonies round, entire, discrete, convex, varying in size from .1 to .4 mm. in diameter.<br>*Microscopic*—Gram-positive diplococci chains about 4, tending toward lancelot shape at times. | Same.<br>Same, containing gram-negative cocci. | Same.<br>Same, containing cocci more lancelot. | Same as A. |

morphology, biology, biochemistry, and pathogenicity of the bacteria isolated was carefully studied, and comparisons were made under identical conditions with known streptococci isolated from various sources, other than rheumatism.

The results can be briefly represented in the Tables. The letters *A*, *B*, *C*, *D*, represent respectively the four strains of bacteria isolated from typical cases of rheumatism. *X*, *Y*, *Z* represent ordinary streptococci isolated by the author from sources other than rheumatism. *X* was isolated from a case of mastoiditis. *Y* was isolated from a case of pelvic abscess. *Z* was isolated from an ordinary abscess.

It is evident that these pathologic conditions can not possibly be considered as a form of rheumatism, and this is the reason why bacteria from these sources were chosen for comparison.

### MORPHOLOGY

It is evident that from the point of view of morphology the above rheumatic strains represent nothing characteristic, the only difference being that in the rheumatic strains the cocci are smaller, and the chains are shorter.

### CULTURAL CHARACTERISTICS

The bacteria were inoculated on the various media and studied both under aerobic and anaerobic conditions. The temperature of incubation was 37.5° C. The reaction of the media employed was 0.9 per cent acid.

A study under low power objective 16 mm., Ocular 4, of colonies, *aerobically* grown 24 hours at 37.5° C. on agar plates in streaks showed the following:

*Macroscopically*.—Colonies were small 1/10 to ½ mm., discrete, convex, raised, glistening, round, following line of streak.

*Microscopically*.—Round, edge entire, but faint, granules very coarse in center of colonies but getting fine towards edge. In center granules clumped together giving nucleated appearance, from which joint granules branch out in branches or strings towards the periphery.

After six days the growth was more profuse but of the same character. Litmus milk of C readily formed acid but only coagulated of three days.

### ANAEROBIC CULTURAL CHARACTERISTICS AND MORPHOLOGIC STUDIES OF STRAINS A, B, C, D

The method employed was that of Buchner, the media exactly the same as for the aerobic cultures, the incubator temperature 37.5° C.

The bacteria grew almost as readily under anaerobic as under aerobic conditions. The growth however was a little slower and not quite so profuse. The bacteria are therefore facultative anaerobes. The anaerobic cultural characteristics are identical with those of the aerobic, and it will therefore be unnecessary to repeat the description. Morphologic studies of all cultures revealed gram-positive diplococci with tendency towards short chain formation.

Streptococci strains X, Y, and Z were cultured both aerobic and anaerobic under exactly the same conditions, and on the same media as strains A, B, C, and D. Strains X, Y and Z exhibited the usual cultural characteristics of

ordinary streptococci, and I therefore deem a detailed description of these unnecessary.

### MORPHOLOGIC AND BIOLOGICAL DIFFERENCES BETWEEN STRAINS A, B, C, D, AND X, Y, Z

The main difference between the various strains of bacteria isolated from cases of rheumatism and the streptococci X, Y, Z were that the former were smaller and appeared mainly as diplococci with a slight tendency toward chain formation. On the other hand, the streptococci invariably appeared in long chains. Strain B appeared in long chains when grown on glucose bouillon, mannit, and salicin. On inulin, strains C and D caused fermentation (D only very slightly), A and B did not. None of the streptococci fermented inulin. The strains A, B, C, D grew *much more* rapidly and profusely than did X, Y, and Z. Under anaerobic conditions this contrast was even greater. Whereas the rheumatic strains grew almost as well under anaerobic conditions as under aerobic, the streptococci on the other hand, grew but sparsely and the majority of the cultures presented no growth at all. On litmus milk the contrast was marked, the rheumatism strains acidified and coagulated the media within 24 hours. You could turn the test tube upside down. The acid formation was very marked. On the other hand the streptococci X, Y, Z turned the blue litmus red but slightly and did not coagulate the milk. The acid formed was but slight. The changes in McConkey's media produced by the micrococcus rheumaticus is regarded as characteristic by Beattie.

The streptococci X, Y, Z would not grow upon this media.

### BIOCHEMISTRY OF STRAINS A, B, C, AND D

The biochemistry of these microorganisms was extensively investigated for me by Dr. Leopold Rein. A summary of his conclusions to date was the following:

1. Absence of lactic acid in all cultures.
2. All bouillon media tubes and bouillon culture tubes give the same findings; viz., the acidity in terms of formic acid as 0.1.

### DRYING EXPERIMENTS

These were conducted only with strain A of the rheumatism series, and X, Y, and Z of the streptococcus series. On June 3, 1910, a slant agar culture of Strain A was left at room temperature. The test tube was simply plugged with the ordinary cotton plug. By Dec. 1, 1910, all the agar in the test tube had dried up and a mere yellowish streak at the inside of the test tube was all that was left of the culture. I attempted to make spreads of the culture on glass slides but this was found physically impossible on account of the dryness of the media. I then poured some sterile plain bouillon into the test tube containing the dried culture and incubated at 37.5° C. At the end of 24 hours, to my great surprise, there was a profuse growth of gram-positive diplococci which had all the characteristics of the original strain A. This microorganism was

still viable after drying for six months. I repeated this drying experiment and found the microorganism viable after drying for 11½ months. For a nonspore-bearing microorganism this resistance to drying is certainly unique. The streptococci X, Y, and Z, on the other hand would die unless transplanted every four to seven days.

ANIMAL EXPERIMENTATION

EXPERIMENT 1.—The microorganisms were grown on glucose agar and a saline emulsion was made of a 24-hour profuse growth, and injected intraperitoneally into *white rats*. The results can be best expressed by Table III

TABLE III

| BACTERIAL STRAIN | *Rheumatic Strains* | | | | *Ordinary Streptococcic Strains* | | |
|---|---|---|---|---|---|---|---|
| INOCULATED | A RAT 1 | B RAT 2 | C RAT 3 | D RAT 4 | X RAT 5 | Y RAT 6 | Z RAT 7 |
| Condition of rat | | | | | | | |
| 8/5/10 | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| 8/6/10 | " | " | " | " | " | " | " |
| 8/7/10 | " | " | " | " | " | " | " |
| 8/9/10 | " | " | " | " | " | " | " |
| 8/10/10 | " | " | " | " | " | " | " |

*Result.*—The rats were observed very carefully for 25 days and found absolutely normal. Neither the rheumatic nor the streptococcic strains had any effect on the rats.

EXPERIMENT 2—

(a) Animals employed, 7 rabbits.

(b) Inoculation, intravenous.

(c) Cultures, saline emulsion of two 24-hour glucose agar growth.

(d) Date of inoculation, Aug. 10, 1910.

TABLE IV

| BACTERIAL STRAIN | *Rheumatic* | | | | *Streptococcic* | | |
|---|---|---|---|---|---|---|---|
| | A RABBIT 1 | B RABBIT 2 | C RABBIT 3 | D RABBIT 4 | X RABBIT 5 | Y RABBIT 6 | Z RABBIT 7 |
| Condition of rabbit | | | | | | | |
| 8/10/10 | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| 8/11/10 | " | " | " | " | " | " | " |
| 8/12/10 | " | " | " | " | " | " | " |
| 8/13/10 | " | " | " | " | " | " | " |
| 8/14/10 | " | " | " | " | " | " | " |
| 8/15/10 | " | " | " | " | " | " | " |
| 8/18/10 | " | " | " | " | " | " | " |
| 8/20/10 | " | " | " | " | " | " | " |
| 8/22/10 | " | " | " | " | " | " | " |
| 8/25/10 | " | " | " | " | " | " | " |

*Result.*—The rabbits were carefully observed for 20 days and all were found absolutely normal.

EXPERIMENT 3.—

(a) Animals employed, 7 guinea pigs.

(b) Inoculation, intraperitoneal.

(c) Culture. 24-hour glucose bouillon.

(d) Date of inoculation, Aug. 17, 1910.

TABLE V

| BACTERIAL STRAIN CONDITION OF GUINEA PIG | A GUINEA PIG 1 | B GUINEA PIG 2 | C GUINEA PIG 3 | D GUINEA PIG 4 | X GUINEA PIG 5 | Y GUINEA PIG 6 | Z GUINEA PIG 7 |
|---|---|---|---|---|---|---|---|
| 8/17/10 | Normal | Normal | Normal | Normal | Normal | Normal | Normal |
| 8/18/10 | " | Dead | " | " | " | " | " |
| 8/19/10 | " | | " | " | " | " | " |
| 8/19/10 | " | | " | " | " | " | " |
| 8/20/10 | " | | " | " | " | " | " |
| 8/21/10 | " | | " | " | " | " | " |
| 8/22/10 | " | | " | " | " | " | " |
| 8/23/10 | " | | " | " | " | " | " |

*Result.*—The guinea pigs were observed for 25 days and found to be absolutely normal with the exception of guinea pig 2, which was inoculated with strain B. This pig was found dead 24 hours after the inoculation.

Autopsy of guinea pig 2 revealed a peritonitis which was caused by a Gram negative, nonmotile bacillus—contamination.

EXPERIMENT 4.—With strain A.

(a) Animal employed, young Newfoundland dog weighing about 80 to 90 pounds.

(b) Inoculation, intravenously.

(c) Culture, 24-hr. glucose bouillon culture.

(d) Date, Feb. 24, 1910, at 3 P.M.

Within 24 hours the dog developed stiffness and tenderness of the left knee joint. The next day the right knee joint became stiff and exquisitely tender. This stiffness and tenderness spread to the joints of the other extremities, so that in an attempt to walk the dog limped markedly. The joints felt hot. The animal was very thirsty, refused nourishment, perspired profusely and was very weak. His temperature ranged between 101-102° F. The dog was irritable and cried a great deal apparently from intense pain. This noise became so troublesome that it was necessary to kill him.

*Autopsy of Dog.*—On Feb. 28, 1910, at 4 P.M. dog was chloroformed. Autopsy revealed the following: All the large joints of the extremities were involved. The joints when opened showed a small amount of gelatinous, clear, viscid fluid and the blood vessels were injected.

The pericardium was inflamed and showed a large amount of fluid slightly tinged with blood.

The heart was otherwise normal and no lesions of the endocardium were demonstrable. The remaining organs revealed no pathologic changes.

*Spreads* from

(a) Joints showed gram-positive diplococci which had no capsules. There was also an occasional lymphocyte and polymorphonuclear leucocyte.

(b) Pericardial fluid—diplococci and streptococci and an occasional red blood cell.

*Cultures* from

(a) Blood of heart and veins showed short chains of streptococci.

(b) Pericardium—Streptococci of moderate and even long chains.

(c) Joints—Diplococci. The microorganism isolated showed in the main the same histologic characteristics of the original strain A with which the dog had been inoculated.

(d) Gram-positive diplococci were demonstrable within the tissues of the synovial membrane.

## CONCLUSIONS

1. In some cases of acute articular rheumatism a microorganism can be isolated from the blood.

2. The reason that the positive blood cultures are not found more frequently in acute articular rheumatism is perhaps because the bacteria tend to

localize in Aschoff's nodules, and except in very virulent forms of the disease are rapidly destroyed in the circulation.

3. The microorganism isolated resembles a streptococcus.

4. Whether McConkey's bile salt media can be used as a differential media to exclude streptococci as claimed by Beattie must yet be proved. For we know that the streptococcus group is not only a large but a very variable one.

5. The resistance of the isolated microorganism to drying is certainly unique for a nonspore-bearing bacteria, particularly for a streptoccocus.

6. Acute articular rheumatism, with its frequent complication, pericarditis, has apparently been reproduced in a dog, by an organism isolated from the blood of a patient suffering from a similar disease.

7. The reason why the other animals failed to contract the disease may have been due to

(a) Lack of susceptibility on the part of the animal.

(b) Attenuation of the microorganism or

(c) Both factors.

8. Morphologic identification of the microorganism is unreliable, since the diplococcus on some of the media will grow in long chains.

9. Further studies are necessary to determine whether acute articular rheumatism is caused by a specific microorganism, particularly immunologic investigations which are under way.

I have purposefully refrained from referring to the literature on this subject since my desire was to describe only my own personal experience.

The cases mentioned came from Dr. Merzbach's service at the Brooklyn Jewish Hospital.

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## MASSIVE INFARCTION OF SPLEEN WITH REPORT OF A CASE*

By DeWayne G. Richey, Pittsburgh, Pa.

AT the autopsy table, infarction of the spleen is not infrequently encountered. The anatomical explanation of this appears to lie in the fact that the comparatively large splenic artery rapidly divides into numerous small terminal branches, possessing small lumina. The infarcted areas may be large or small, single or multiple. The multiple ones are usually small, although this does not necessarily obtain in all instances. Broadly speaking, however, splenic infarcts are larger than those found in other solid viscera, the reason for which again can be attributed to the manner of division of the radicals of the splenic vessels. When the infarcted area is small, it retains the wedge-shaped appearance, with the base directed toward the capsular surface. But if the infarct is quite large, say, involving more than one-fourth the organ, its typical shape is lost, and it becomes more irregular in outline, causing a subsequent distortion of the spleen. Moreover, splenic infarcts, as a rule, extend to the capsule of the

*From the Magee Pathological Laboratories, Mercy Hospital, Pittsburgh, Pa.

organ, in contradistinction to some renal infarcts, for instance, which may be completely surrounded by living kidney tissue. The reason for this is, no doubt, that the capsular arterial distribution to the kidney does not find its analogue in the spleen.

Extensive infarcts of the spleen are by no means rare, yet it is unusual to have the entire organ incorporated in the infarcted zone. In recent years evidence has been produced which will readily account for this condition. Warthin called attention to the splenic anastomoses with the gastroepiploic vessels in the omentum gastrosplenicum, and later, Troell referred to an additional factor, that many broad, transverse anastomosing channels exist between the branches of both the splenic artery and vein, located close to the hilum of the organ. With this anatomical arrangement, it would necessitate either a very extensive blockage of the splenic blood channels or a gross anomaly associated with a lesser obstruction, to render virtually the entire spleen one huge infarct.

When massive infarction of the spleen does not occur, even the bland variety, if the condition is not recognized clinically and removed by operation, the result may be rapidly fatal. The findings of an old infarct involving practically the entire spleen, having occasioned no discomfort to the patient, and having played no direct part in his death, is rather a unique condition. In view of the fact that there is a paucity of references to similar conditions in the literature, particularly when contrasted with the correspondingly many allusions to other splenic processes, it was deemed worthy to report the findings in such a case.

The following case was admitted to the Mercy Hospital, Pittsburgh, Pa., on Jan. 12, 1917. It was assigned to the service of Dr. T. S. Arbuthnot, to whom I am indebted for the clinical records:

R. C., male, age 35, Negro, laborer, Hosp. No. 4648-17. On admission the patient was in a semicomatose state, so that a history from him was not available. Unfortunately the social status of the patient was such that no additional data could be obtained, save for the knowledge of a long standing deafness, and that the onset of the present illness had begun one week previously.

It was with the greatest difficulty that the patient could be aroused from his semicomatose condition, and at no time was he able to orientate himself. He presented a marked generalized hypertonicity, associated with extreme retraction of the head and rigidity of the neck.

Considerable pain was occasioned by movement of the head and by pressure over the tip of the left mastoid process. Deafness was quite obvious. The eyes were fixed and staring; the pupils equal, dilated, slightly irregular in outline and static. Thoracic examination revealed no essential organic lesions in the lungs or in the heart.

The abdomen was distended, very tense and both recti were rigid. There was no evidence of fluid in the peritoneal cavity, the spleen was not palpable. All reflexes, both superficial and deep were greatly exaggerated, but equal. Kernig's sign was definitely positive. No paralyses could be elicited. The temperature ranged from 102° to 104° F.; the pulse from 120 to 150; the respirations from 28 to 46. The blood pressure fluctuated within normal limits, around 100 (S.B.P.) and 80 (D.B.P.) mm. Hg. The blood count was as follows: R.B.C., 4,900,000; W.B.C., 45,100; Hgb. 88 (Sahli). Stained smears exhibited a marked polycytosis, (95 per cent), with a corresponding decrease in the lymphocyte forms. Analysis of a catheterized specimen of urine was negative. On lumbar puncture a turbid, almost milky, spinal fluid, under definitely increased tension, was recovered. Pneumococcus, Type IV, was isolated from the culture.

Despite vigorous eliminative and supportive measures, the patient pursued a rapidly fatal course, dying within 18 hours after admission, the clinical diagnosis was pneumococcic meningitis.

An autopsy was performed two hours after death by Drs. W. W. G. Maclachlan and DeW. G. Richey.

To obviate the rehearsal of a lengthy protocol, only the outstanding features of the autopsy findings both macro- and microscopical will be mentioned. Particular attention, however, will be paid to the spleen.

The body was that of an adult male negro, measuring 161 cm. in length. The body was well developed and well nourished. The head was markedly retracted. The entire surface of the brain was covered by a diffuse, greenish, adherent exudate, particularly well marked in the sulci, and as abundant anteriorly as it was posteriorly. The basilar region of the brain was bathed in a greenish, purulent cerebrospinal fluid. All the sinuses of the dura were clear. The left middle ear and the mastoid cells were filled with a gelatinous, pink, rather soft granulation tissue. The lungs exhibited no areas of consolidation, fibroses, or calcification. The heart valves were clear, presenting no acute, or chronic lesions. There was a moderate degree of cloudy swelling of the heart, liver and kidneys. The aorta, pancreas, adrenals, bladder and testes revealed nothing unusual.

A cursory examination of the splenic fossa gave the impression that the spleen was entirely absent. It was found, however, in the left hypochondrium, being 3.5 cm. above the upper pole of the left adrenal, and was imbedded in a dense layer of adipose tissue. Its only abnormal attachment was to the left parietal peritoneum, by several dense adhesions. The left border of the great omentum which was curled upward, spread outward in a fan-shaped manner, to its insertion along the mesial surface of the organ. Unfortunately, the splenic vessels were not dissected at this time, nor was the lumen of the splenic artery probed. No accessory spleens, enlarged lymph glands, nor hemolymph nodes were encountered.

*Spleen.*—Weight 25 grams. Measured 4.8 x 2.2 x 1.8 cm. The spleen was exceedingly small and had completely lost its normal appearance, being devoid of any of the gross landmarks by which it could be identified as such. Its removal with the perisplenic omental tissues, which was accomplished only with difficulty, revealed a very unique structure. It consisted of a large, oval nodule, with a dull, yellowish surface, and was very hard in consistency. At one end of the nodule, there were three irregularly oval lobulated masses, varying in size from 1.2 by 0.9 by 0.4 to 1.7 by 1.2 by 0.9 cm. Beneath the thickened capsule, these presented a reddish gray appearance, which simulated somewhat the color of splenic tissue. At the opposite end of the central nodule was a thin, fin-shaped piece of compressed tissue, measuring 4 by 2 by 0.2 cm. The surface was smooth, and it presented a dull, dark red appearance, beneath which several arborescent trabeculations could be seen. This piece of tissue was of approximately the thickness of the diaphragm, and looked not unlike that structure, but also suggested a splenic origin, inasmuch as the cut surface revealed a dull, red, meaty appearance, in which the cut mouths of the blood vessels were clearly observed. The entire organ, then presented three separate and distinct parts—(1) the nodular, hard center, which was the largest part; (2) the lobulated, glandlike nodules at the lower pole; (3) the flattened fin-shaped tissue at the opposite pole.

On section through the organ, the central nodule was seen to consist of a yellowish, necrotic material, through which numerous dense strands of fibrous tissue coursed in an irregular fashion. Here and there, tiny granules of calcified material could be made out. At one place near the center, a small oval island of reddish tissue occurred, which bore a close resemblance to the tissue noted at one end of the specimen. This area measured on the cut surface, 6 by 2 mm.

The appearance of this mass suggested a process of necrosis, with subsequent fibrosis and calcification, following extensive infarction of the organ. The cut surface of the three nodules previously described presented a dull red, smooth, glistening appearance, in the center of which was a stellate, white, fibrous core, from which radiated numerous fibrous trabeculae. These nodules communicated with each other and, because of this fact, although they closely resembled splenic tissue, they did not convey the impression of accessory spleens, but rather a portion of the organ which had survived by virtue of the adhesions which were present at this point.

Microscopic section of the spleen showed, along one border, a narrow strip of splenic tissue. This area revealed the usual picture of splenic pulp, except that there was a marked increase in the fibrous connective tissue. The capsule was markedly thickened. It contained many small blood vessels. The sinuses of the splenic pulp were dilated and in them could be seen erythrocytes, endothelial cells, lymphocytes and leucocytes. Of the

latter, the polymorphonuclears remained. Only vestiges of the lymphoid tissue of the organ remained. One small Malpighian corpuscle was noted. Immediately contiguous with this area, and sending broad, irregularly arborescent ramifications into it, could be seen a wide expanse of tissue, densely fibrous in appearance. This area was composed of variously-sized islands of hyaline material, which were supported by a dense fibrous stroma. In the section no evidence of calcification was present, though the character of the tissue was such that it might well have been expected. In curious cleftlike interstices in this solid fibrous tissue, masses of brown crystalline pigment in large masses, were noted. The large masses had provoked giant-cell formation, of the foreign body type, while smaller particles lay in endothelial cells. There was no evidence of tubercle formation. Cultures taken from the heart's blood and meninges, at autopsy, showed the pneumococcus; the culture from the mastoid showed, in addition to this organism, the staphylococcus pyogenes aureus, and B. pseudo-influenzæ. All the strains of pneumococcus which were isolated, fermented lactose, salicin and inulin, and belonged to Group IV.

The anatomical diagnosis can be condensed to the following: acute suppurative meningitis (pneumococcic); acute and chronic suppurative otitis media (left); acute and chronic suppurative mastoiditis (left); cholelithiasis; massive infarction of spleen; atrophy of spleen; chronic perisplenitis.

In summarizing the case, we have a male negro, 35 years of age. He was admitted to the hospital in a semicomatose state. The only available history was that of a protracted deafness and that the onset of his present illness had antedated his death by a period of eight days. There was no history, or antemortem, physical or laboratory finding which pointed to the presence of any splenic condition. The cause of death was directly referable to an acute suppurative meningitis (pneumococcic), the origin of which was an old otitis media and mastoiditis. The spleen was very atrophic, showing a large area of necrosis, fibrosis and calcification, and two small peripheral masses of living splenic tissue surrounded by dense fibrous adhesions. The positive findings in the other viscera were coincidental to the acute infection of the meninges, save for the presence of many small gall-stones. No focus from which an embolus could have arisen was found. No congenital abnormalities were evident.

Absence of the spleen may be a congenital anomaly or the result of surgical intervention and is not incompatible with life. Hodenpyl, in reporting a case of apparent absence of this organ, was able to collect nine other cases from the literature. Others have cited instances where a congenital absence occurred in monsters, notably Hensinger and Potter. The three most common findings associated with splenic agenesis are accessory spleens, generalized lymphatic hyperplasia and hemolymph nodes. The accessory spleens may vary from one to fifty, as cited by Thorel, or 400, as mentioned in the case of Albrecht. The marked generalized lymphatic hyperplasia was one of the outstanding features of Hodenpyl's case. The occurrence of hemolymph nodes is probably closely analogous to this phenomenon, for, as Warthin has pointed out, these structures apparently simulate lymph-glands in function.

References to diminutive spleens are not commonly encountered in the literature. Calvert reports the case of such a spleen weighing 2.1 grams, which was removed at autopsy from a female 30 years of age. Microscopically, a diminished splenic pulp, thickened arterial walls and trabeculae were the main considerations. Glinski found a small spleen at necropsy in a female, aged 45, who died of pulmonary tuberculosis. The condition, he intimates had no bearing on the size of the spleen, but offers no explanation regarding the etiology

of the splenic finding. Paulesco records the case of "rudimentary spleen," measuring 5 by 1 by 2.6 cm.

Again, one encounters but few cases of extensive infarction of the spleen, with marked atrophy. Vintele apparently encountered such a case, but his article was not obtainable at this time. Nuzum, in a recent communication on infarction of the entire spleen, was able to collect twenty-eight cases in the literature, to which he added four of his own. In only two of the entire series of cases were the spleens small, and in only one, that of Durand, could the finding be compared with our case. In this instance the organ was described as a "gigantesque cicatrix." In all the other cases the spleen was enlarged, being in one case as heavy as 2700 grams and in another as large as 25 by 15 by 8 cm. There is but little doubt that the variations in the proportions of the organs in this series and ours could be adequately explained from the standpoint of time rather than the amount of involvement or the manner in which the infarction occurred. As Nuzum points out, the atrophic and fibrosed spleens represent the final stage in the process of repair of the infarcted area. It is imperative, if there be a culmination of the process in cicatrization, that the etiologic factor be of a sterile nature, and, but to a lesser extent, of a gradual onset. Rapid occlusion of both splenic vessels leads almost without exception to a fatal termination, if the causative agent is infective through abscess formation or through absorption of the toxic products of cellular disintegration, if the agent be sterile. Hence, progressive thrombosis of both the splenic artery and vein is the probable mode of development of the lesion in our case, for, as Nuzum's examples would indicate, an embolus of the splenic artery rarely causes infarction of the entire spleen.

The various stages through which a bland infarct passes has always been a subject of great interest. Whether in its incipiency, an infarct is hemorrhagic or anemic has called forth considerable debate among many ardent workers. Some writers, notably Beckman and Weigert, followed by von Recklinghausen, Thoma and Orth, held the latter view and Uhthoff, Talma, Beattie and Dickson, and others, accepted the former theory. In later years, Karsner and Austin, arrived at the same conclusions, following a series of experiments on dogs. In any event there seems to be but slight doubt that whether an early infarct is hemorrhagic or anemic depends largely on the organ involved. Thus, infarcts of the retina and kidney are usually anemic, those of the lungs and intestines are practically always hemorrhagic. When hemorrhage does occur, it is usually by a process of diapedesis rather than rhexis. Welch and Mall hold that a high venous pressure favors hemorrhage in the infarcted area while a low arterial pressure opposes it. It is highly probable that the whole story is not told from the point of view of pressure in the circulatory channels. As Adami points out, another important factor must be taken into consideration, namely the susceptibility of certain tissues to circulatory unrest, with a rapid discharge of autolytic enzymes, and liberation of prothrombin, so that coagulation occurs before diapedesis of the erythrocytes can take place. It seems logical to conclude with MacCallum, that death of the tissue in the area of infarction is due to the anemia. In our case the presence of considerable blood pig-

ment would indicate that there had been a considerable extravasation of blood into the infarcted area.

A consideration of the minutiæ of the specimen we have described, reveals no characteristics which differ from the usual end results of bland infarcts. Of far more interest is the persistence of some of the splenic tissue. A concomitant perisplenitis is the usual finding in splenic infarcts due to irritation of bacteria or tissue disintegration. In the earliest stages a fibrinous exudate occurs, which later becomes organized. The omentum becomes adherent to the splenic surface, or, if the process is sufficiently extensive, may envelop the entire organ. This fact was noted by Troell, who found the spleens of two guinea pigs markedly diminished in size after ligation of the splenic vessels, despite the fact that in both instances the organs were enveloped in omentum. From this observation he concludes that a "subsidiary collateral circulation through the spleen capsule could not be developed and thus compensate the stoppage of the blood supply through the spleen hilum." This same author cites the instance of some experimental work carried on by Garlow and Sheldon, who ligated the entire hilum in three dogs, all of which died. The latter worker, subsequently followed Pirone's method of attaching the omentum to the spleen. Again, all the animals died. On the other hand, Jamison observed that, in ligating the splenic pedicle in five dogs and covering the spleen by omentum, all the dogs recovered, there was no severe crisis, as seen in the cases where the omentum was not attached, and the degree of atrophy was greater. The results of these investigations are widely divergent. From the data on hand it would be difficult to draw any conclusions as to the function that the omentum plays in this type of case.

The author wishes to thank Doctor Oskar Klotz for many valuable suggestions during the preparation of this paper.

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# THE ETIOLOGY OF SCARLET FEVER*

## II. A Skin Test Which May Indicate Immunity to Scarlet Fever

By R. W. Pryer, D.P.H., and George Sewell M.D., Detroit, Mich.

IN a previous paper[1] from this department, mention was made of a large organism which was isolated from the blood in a fatal case of scarlet fever,—to summarize briefly:

This organism varies in length from 2 to 8 microns and seldom exceeds 4 microns in diameter. In young cultures the organism tends to be spherical in shape. It stains readily and tends to be gram-negative although its behavior to Gram's stains is not constant. With a differential stain such as Giemsa's, a red granule can be made out in a faintly staining central portion. This organism grows best on blood agar and cultures on this media give a peculiar distinctive odor. The growth in liquid media is very slow, no pellicle is formed but a slimy sediment gradually collects. In sugar media no gas is formed and alkali is slowly produced. Gelatin is not liquefied.

It is not our intention in this paper to go deeper into the cultural characteristics of this organism but in the near future we expect to present an article on this subject and desire to state at this time that we have obtained this same organism from the throat of scarlet fever patients, although only in a very limited number of cases. Cantacuzene,[2] however, has described an organism similar to, if not identical with, the one described by us and states that while ordinary laboratory animals are immune to injections of these cultures, the injection into monkeys is followed by sickness and occasional death. The condition produced in monkeys is very similar to the clinical manifestations of scarlet fever in the human.

The skin test reported in this paper is based largely on the work of Gay[3] and his associates on the typhoidin test in typhoid fever. Typhoidin is prepared by evaporating a broth culture of B. typhosus at 56° C. to about 25 per cent of its original volume. This concentrated culture is then precipitated by slowly pouring into an excess of absolute alcohol. The precipitate is filtered off, washed in absolute alcohol, then with ether, dried, and finely pulverized in a mortar. The use of polyvalent preparation of typhoidin is recommended and the dose is given in the literature as 0.00002 gm.

It seems to us as though no definite dosage could be given for a preparation of this kind. We have found in our work that the dose of these preparations varies within wide limits and must be determined for each one just as it is necessary to determine the M.L.D. of each batch of diphtheria toxin and to carefully standardize each new antigen.

Typhoidin when injected intradermally into people who have had typhoid fever gives a distinct reaction in about 75 per cent of the individuals and this

*From the Bureau of Laboratories of the Detroit Board of Health.

reaction persists for over forty-eight hours. In people who have been recently vaccinated against typhoid fever, the percentage of positive reaction is slightly lower, whereas in individuals with no history of typhoid fever, the percentage of positive reactions is only about 14.

Although we realize that we have not proved that this organism which for the sake of convenience we will refer to as B.B., is the cause of scarlet fever, we have called the preparations made from it scarlatin and in this paper we use that term to describe the material made from these cultures in a method similar to the manufacture of typhoidin from the typhoid bacillus.

The growth of the organism isolated by us is very slow in any liquid media, consequently in order to get a heavy growth in broth considerable time is required. Our first scarlatin (Scarlatin 1) was prepared from a culture of B.B. No. 1, which had been growing in broth for eighty days. This preparation was accidentally destroyed before standardization was completed but gave results which encouraged us to proceed with this work.

Scarlatin No. 2 was also made from culture B.B. No. 1. The broth used was made from fresh beef and contained 2 per cent Difco peptone, 1 per cent glucose, 0.5 per cent salt and was adjusted to a final reaction of +1 by phenolphthalein. This flask was incubated for 70 days at 37° C.; at the end of that time the media had evaporated to about 25 per cent of its original volume. The growth of organisms was heavy and slimy and had settled to the bottom of the flask. The growth was proved to be pure by subculturing and microscopic examination. This growth was poured into 20 volumes of absolute alcohol, stirring continually. The precipitate formed was too sticky to filter and was separated by centrifuging. The precipitate was washed with absolute alcohol, then with ether by shaking in the tube, dried at 37° C. and then finely pulverized in a mortar.

Upon standardization of Scarlatin No. 2, 0.00002 gm. was found to be what we call the minimum effective dose; i. e., that amount which upon intradermal injection will give the highest number of positive reactions in scarlet fever convalescents and the lowest number in individuals with no history of scarlet fever. The solution for the test was made up so that this amount by weight of the power was contained in 1/10 c.c. of sterile physiologic salt solution. This amount was injected intradermally into scarlet fever convalescents and into people who gave no history of scarlet fever.

These injections were controlled by the use of a preparation of sterile broth evaporated to 25 per cent of the original volume and precipitated by absolute alcohol. The precipitate was washed with absolute alcohol and with ether, then dried and pulverized. The dose of this control has been the same amount as the scarlatin preparation and has been given into the other arm.

Table I shows the results obtained in a series of cases with Scarlatin No. 2. The patients with history of scarlet fever were patients in the scarlet fever pavilion of the Detroit Municipal Hospital and were in from the third to the fifth week of the disease. The control cases were patients who were in the same hospital but in different pavilions and were convalescent from other diseases. Most of these were about to be released after diphtheria.

TABLE I

| | No. | + | ? | − | % + |
|---|---|---|---|---|---|
| Scarlet fever | 34 | 25 | 1 | 8 | 86 |
| Not scarlet fever | 35 | 4 | 3 | 28 | 11.5 |

These reactions were read at the end of twenty-four hours. A reaction is called positive when the area of inflammation is as large as a dime (about 18 mm. in diameter). Reactions recorded as questionable have a definite redness about the site of inoculation. Induration at site of inoculation without definite inflammation is recorded as negative.

This material appears to retain its potency indefinitely in the dry powdered state but when put in solution, deteriorates rapidly at room temperature. When kept in the ice box, the solution increases somewhat in strength at first and then gradually deteriorates.

Table II shows the results obtained with Scarlatin No. 2 on a few normal individuals:

TABLE II

| | No. | + | − | % + |
|---|---|---|---|---|
| History of scarlet fever | 2 | 2 | 0 | 100 |
| No history of scarlet fever | 4 | 2 | 2 | 50 |

It is our opinion that many people have had scarlet fever and are not aware of it. Farther on in this paper we will go deeper into this but we desire to state here that the two people with no history of scarlet fever who gave a positive reaction with Scarlatin No. 2 are much older than the other two. It is of course well known that older people are less liable to scarlet fever than children or young people.

In repeating this work a flask of media of the same composition but freshly made up was inoculated with the organism B.B. No. 1, and after three days in the incubator, this was concentrated and precipitated as before. This preparation was nearly inert, although by this time the organism was growing fairly well in liquid media. This preparation which we have labeled Scarlatin No. 3 is too weak.

Scarlatin No. 4 was made in the same way from a culture nine days old. This preparation, while not as strong as No. 2, seemed to give very good results. The following shows the standardization of this product.

In the first set of experiments 2 mg. of the powder was weighed out very carefully and then ground in a sterile mortar with 80 mg. of sodium chloride. Ten c.c. of water was added in small portions, stirring after each addition. 1/10 c.c. of this solution was then injected intradermally.

Four scarlet fever patients and five others with no history of scarlet fever received this injection. None reacted.

In Table IV, the weight of scarlatin was increased to 5 mg. With a dose of 1/10 c.c., this is, of course, equivalent to .00005 gm. Again there were no reactions in either series.

The use of 10 mg. of powder with 80 mg. of salt in 10 c.c. of water has been the strength used in the following experiments. In most of these, a control injection has been made into the other arm, either of the same amount of culture media as heretofore described, or a typhoidin solution.

The typhoidin used was prepared from the Rawlins strain of B. typhosus according to the method described by Gay and his associates. We have not attempted to standardize this for the determination of immunity to typhoid fever, and all our reactions were read at twenty-four hours instead of the forty-eight-hour period recommended by workers with typhoidin.

Our object in using typhoidin in this work has been to see if scarlet fever left a hypersensitive condition of the skin. We do not believe that it does, but we have, we believe, shown that in the use of scarlatin on one arm controlled by an injection of typhoidin in the other, the reactions of each preparation are intensified and that such compared injections give misleading results.

In Table III the scarlatin used was No. 4 in 1/10 mg. dose. Part of these injections were controlled by an equal amount by weight of culture media control. Part were controlled by the use of typhoidin in 0.0000025 gm. doses. A few were not controlled at all. When a control was used it was always given intradermally into the right arm, the scarlatin being given in the left.

TABLE III

SCARLATIN TESTS

| | No. | + | ? | − | % + |
|---|---|---|---|---|---|
| Scarlet fever convalescents 2nd to 5th week | 42 | 22 | 2 | 18 | 52.5 |
| No history of scarlet fever | 31 | 5 | 2 | 24 | 16.1 |

In Table IV Scarlatin No. 4 in the same dose was used either alone or with culture media control. All controls in this series were negative.

TABLE IV

| | No. | + | ? | − | % + |
|---|---|---|---|---|---|
| Scarlet fever convalescents 2nd to 5th week | 29 | 15 | 2 | 12 | 51.5 |
| No history of scarlet fever | 21 | 0 | 1 | 20 | 0 |

In Table V, the results with typhoidin are given in a series of cases. Part of these have had at the same time an injection of scarlatin in the other arm.

TABLE V

| | No. | + | ? | − | % + |
|---|---|---|---|---|---|
| Scarlet fever convalescents 2nd to 5th week | 31 | 23 | 5 | 3 | 74 |
| No history of scarlet fever | 24 | 20 | 3 | 1 | 83.5 |

In Table VI the results with typhoidin alone are shown. These reactions were not controlled.

TABLE VI

| | No. | + | ? | − | % + |
|---|---|---|---|---|---|
| Scarlet fever convalescents 2nd to 5th week | 13 | 9 | 2 | 2 | 69 |
| No history of scarlet fever | 14 | 11 | 2 | 1 | 79 |

Scarlatin No. 5 was prepared as follows: 100 c.c. 18-day broth culture of Organism No. I; 100 c.c. 18-day broth culture of Organism No. II and 100 c.c. 70-day broth culture of Organism No. II, were combined and evaporated at 56° C.

The 100 c.c. of broth in which Organism No. II had been growing for 18 days had comparatively few organisms in it while the others had a very heavy

growth. All cultures were subcultured and proved to be pure strains. Organism No. 1 was isolated from the blood, while Organism No. 2 was isolated from the throat of a scarlet fever patient.

Scarlatin No. 5 was prepared from this concentrate in the usual way and standardized; 0.00002 gms. was found to be the minimum effective dose. Table VII shows the results in a small series of tests at the Detroit Municipal Hospital.

TABLE VII

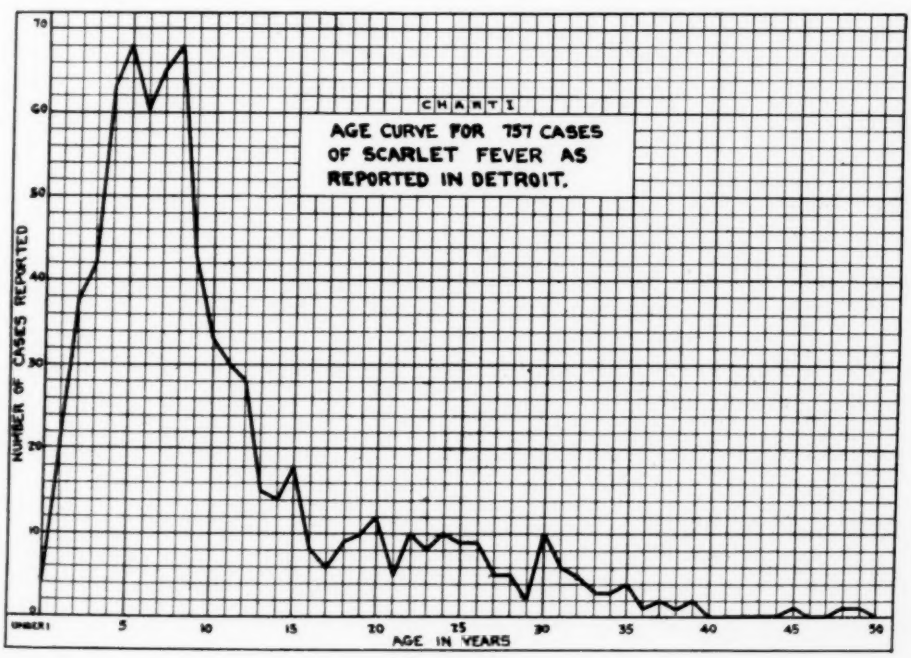
| | No. | pos. | ? | neg. |
|---|---|---|---|---|
| Scarlet fever 2nd to 5th week | 35 | 15 | 14 | 6 |
| No history of scarlet fever | 20 | 3 | 3 | 14 |

Table VIII shows the results obtained in a series of tests with Scarlatin No. 5. The people included in this table were normal people with no infectious disease.

TABLE VIII

| | No. | pos. | ? | neg. |
|---|---|---|---|---|
| History of scarlet fever | 12 | 7 | 3 | 2 |
| No history of scarlet fever | 25 | 5 | 6 | 14 |

It has been noted in this work that in people with no history of scarlet fever the probability of a positive reaction increases with age. Scarlet fever is essentially a disease of childhood. In Chart No. 1 the distribution by ages of the total number of cases of scarlet fever reported in Detroit between Nov. 1, 1917,




and Feb. 28, 1918, is shown graphically by the solid line. A study of this chart shows that of these 757 cases 609 or over 80 per cent are 15 years or less in age and that the highest incidence is between 5 and 8 years of age.

The number of tests on people with no history of scarlet fever is not as great as it should be. Taking those cases on which we have complete data we

have 83. Of these 83, 45 are less than 20 years of age and the reactions were recorded as, positive 6, questionable 5, negative 34. Of the 38 over 20 years of age our records show, 11 positive, 11 questionable, and 16 negative. In the cases with history of scarlet fever, the age did not influence the reaction in this way.

Table IX shows the results with scarlatin tests in scarlet fever convalescents arranged according to duration of the disease in weeks. This seems to show that immunity to scarlet fever is developed rather slowly, which is in agreement with the clinical experiences in this disease.

TABLE IX

| Duration | No. | pos. | ? | neg. | % + |
|---|---|---|---|---|---|
| 2 weeks | 11 | 4 | 0 | 7 | 36.3 |
| 2 to 4 weeks | 25 | 11 | 8 | 6 | 44. |
| Over 4 weeks | 25 | 14 | 5 | 6 | 56. |

## SUMMARY

In a previous paper an organism of unusual characteristics was described. This organism was isolated from the blood of a man dying of scarlet fever. In this paper mention is made of the fact that we have found this same organism in the throat of scarlet fever patients, although only in a very low percentage of cases studied. Cantacuzene has described an organism found in the throat of scarlet fever patients which is evidently the same as the one described by us and has shown that this organism produces in monkeys a condition closely resembling scarlet fever.

We have shown that a preparation made from these cultures by a method similar to the preparation of typhoidin from the typhoid bacillus gives a higher percentage of reactions in scarlet fever convalescents than is the case in other infectious diseases, while typhoidin gives slightly more positive reaction in other infectious diseases than it does following scarlet fever.

The probability of a positive reaction with scarlatin, as we call this preparation, increases with the duration of disease and in people with no history of scarlet fever increases with age of the individual tested.

We do not hold that we have proved that this organism is the etiologic factor in scarlet fever, but we do believe that we have presented sufficient evidence to give this organism serious consideration as a possible and probable cause of the disease.

To better summarize our work, Table X shows our results with the different preparations in scarlet fever patients, in people with a past history of scarlet fever and in people with no history of scarlet fever infection.

TABLE X

| | No. | pos. | ? | neg. | % pos. | % ? | % neg. |
|---|---|---|---|---|---|---|---|
| Scarlet fever | 125 | 71 | 20 | 34 | 56.7 | 16 | 27.3 |
| No scarlet fever | 115 | 19 | 14 | 82 | 16.5 | 12.3 | 71.2 |

The writers desire to express their appreciation to Dr. A. Lange for his assistance in portions of this work.

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# ADAPTATIONS OF RENAL FUNCTION TESTS FOR GENERAL USE

By Capt. Warren T. Vaughan, M.R.C., U. S. Army*

READERS of the current medical literature are receiving nowadays a vast accumulation of useful information concerning the more recent, so-called "tests of renal function." The technic of the various procedures has been pretty well perfected and the men who are especially interested in the study of the nephritis problem are now busy accumulating data concerning the reactions of these tests in the various types of nephritis and in other diseases. There is therefore today an abundant supply of information upon which we may rely in the interpretation of our results; and the conclusions drawn concerning the functional efficiency of an individual's kidneys are no longer hypothetical but may be based upon knowledge of scientific facts.

In most modern hospitals the "kidney tests" are performed on all cases in which the renal function is in question and some hospitals have gone so far as to make some of them, especially the "phthalein test," practically routine on all cases. A patient who enters a good hospital for medical observation has as thorough an examination of his kidneys as is made of his heart, lungs and digestive system.

Although the examination of a medical case for renal function is usually more satisfactorily conducted in a hospital, modifications of the newer methods may be easily adapted to an office practice. Alert practicing physicians have probably read most of the literature concerning the technic to be followed in hospital examinations, but they hesitate to modify it for office or home use because they are in no position to know how much the changes instituted are going to vitiate the results. The simplifications presented here are the result of an experience with the various tests as modified in the out-patient department of a large hospital.

For the sake of completeness certain rather elementary points will also be emphasized.

A really thorough examination of renal function presupposes in the first place a complete and thorough physical examination, including especially examination of the cardiovascular system, the throat and tonsils, the thyroid gland and the blood. In both hyper-and hypo-thyroidism, in primary or pernicious anemia and secondary anemias, as well as in certain other conditions, there is a demonstrable change in renal function, and it is important to recognize those conditions if present since they form a direct etiology for the kidney damage. Improvement in the condition of the kidneys will follow successful treatment of the other condition present. The frequent occurrence of chronic tonsillitis and other focal infections concomitant with chronic nephritis strongly suggests an infecting agent as a cause of renal damage, while microscopic examination of such kidneys frequently demonstrates the remains of metastatic foci in the

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organs themselves. All sources of local infection should therefore be sought out in the preliminary physical examination of a nephritis suspect. In the cardiovascular system there may be present left cardiac hypertrophy and a ringing aortic second sound, associated with a hypertension. Arteriosclerosis may accompany this picture or may be absent, or may even be present without hypertension. Every case with high blood pressure or arteriosclerosis, or both, should have careful studies of his renal function and in most cases there will be slight, but demonstrable, impairment, while in a few the damage will be very serious. Nephritis is the one particular disease in which the condition frequently progresses entirely insidiously and the patient does not consult the physician until certain symptoms, indicative of very severe kidney damage, finally appear and treatment will be of little or no avail.

### OUTLINE FOR A COMPLETE EXAMINATION OF RENAL EFFICIENCY, APPLICABLE TO PRIVATE PRACTICE

(1) Make a complete routine *physical examination.* Map out the heart borders and note especially the distance of the left border and apex impulse from the mid line, their relation to the nipple line and in what interspace the maximum cardiac impulse lies. Note the character of the heart sounds, especially of the aortic second sound and observe the presence or absence of any murmurs at any of the valve areas.

The radial arteries should be palpated with a view to determining the presence or absence of thickening or of tortuosity. By bimanual palpation of one radial artery the presence or absence of any marked degree of hypertension may usually be determined. The index or middle finger of the left hand is used to exert pressure on the artery while the pulse is noted distal to the point of compression with the same fingers of the right hand. The compression force necessary to cause the pulse to disappear is the criterion sought. After some experience it is possible, as stated, to determine whether or not hypertension be present, but on the other hand, it is an extremely hazardous undertaking to try to estimate the *degree* of hypertension. The brachial and temporal arteries should also be examined for beading, tortuosity and thickening.

(2) *Take the blood pressure,* including both the systolic and diastolic pressures. In a very rough way the systolic pressure is an indication of the heart power and the diastolic indicates the condition of the vessels—of the peripheral resistance. Thus, in aortic insufficiency and hyperthyroidism, there frequently occur rather high systolic pressures with low or normal diastolic pressures. The high diastolic pressure is, therefore, frequently a better indicator of vascular or renal hypertension than is the systolic. A diastolic pressure persistently above 100 mm. Hg is pathologic, while one between 90 and 100 mm. Hg should arouse suspicion and is an indication for repeated examinations. As a rule a high diastolic pressure has associated with it an increased systolic pressure. A persistent systolic pressure of 160 mm. Hg in a young adult is undoubtedly abnormal. It is usually indicative of chronic nephritis and in the U. S. Army it is sufficient to disqualify for active service. It is highly essential to watch for abnormal variations in the blood pressure on different

occasions, particularly an increase of systolic pressure after exercise and excitement. It has been said that the normal average systolic rise after running fifty steps is 24 mm., the diastolic rise is about half as much or 12 mm. The lifting of a 20-pound dumb bell six feet thirty times in sixty seconds will normally cause the systolic pressure to increase about 20 mm. Hg.

(3) *Ophthalmoscopic examination* of the fundi of both eyes will give at once knowledge of the condition of the blood vessels, especially those of the nervous system. In the retina arteries and veins may be observed uncovered by any overlying tissue. They may be straight or tortuous, lined with the perivascular streaking of sclerosis or obliterated. There may be the flame-shaped retinal hemorrhages and the exudations so characteristic of advanced chronic nephritis.

(4) *Examination of a single fresh specimen* of urine should be made. This will include description of color, turbidity, reaction, specific gravity and the presence or absence of albumen and sugar. It frequently happens in cases of chronic nephritis especially of the so-called chronic interstitial nephritis, that albumen is absent from the urine while casts are present in greater or less numbers. For this reason it is essential that examination of the sediment after centrifugalization be made as a routine. Even where a renal damage is not suspected microscopic examination of the urine is indicated in patients giving a history of polyuria, especially of nocturia or showing signs of arteriosclerosis or hypertension and, again, when the urine examination shows a low specific gravity or the presence of sugar or albumen. Cases of nephritis in which albumen is present in fairly large quantities and which show an essentially negative sediment are in a fairly high percentage of histories associated with syphilis, and when such findings are noted a Wassermann reaction is indicated.

(5) *Mosenthal's special two-hour renal test* will be the first special test to be described because it is that test which shows the earliest and slightest degree of kidney damage in chronic nephritis. This test will show positive results at a time when the phenolsulphonephthalein test and the Ambard test will still be essentially negative. The performance of this test is indicated under the same conditions as noted for the examination of urinary sediment in the last paragraph. The finding of casts in the urine is also a direct indication for the test. The complete test consists, briefly, in placing the patient on a special diet in which the intake of salt, protein and water is known and controlled. Urine is collected in separate containers, at two-hour intervals throughout the day, the night output (9 P.M. to 7 A.M.) being collected as one specimen. The specimens which altogether would make one 24-hour collection are now examined separately as regards volume, specific gravity, salt content and total nitrogen content. As a rule the patient has been kept on a standard diet for two or three days preceding the day of the test. In this way the salt and protein intake are known to have been normal previously and there has been no shortage or too great abundance of either one, either of which conditions would tend to alter the results of the test.

In early chronic nephritis the kidney loses the ability to concentrate excreted substances. As a consequence one of the earliest urinary findings in

chronic nephritis is an increase in the fluid output with lowered specific gravity due to the lessened concentration of the solids. The subjective symptoms at this time are those of polyuria and nocturia. Whereas a normal kidney can rapidly relieve the blood of too great a concentration of solids, such as a high sodium chloride content, following a meal containing an excess of salt, by excreting it in high concentration, the damaged kidney has lost that power. When in the noon meal of the test diet an excess of salt is added (up to 6 gm.), the normal kidney responds as evidenced in the examination of the next one or two two-hour urine collections by secreting a urine of high salt content and high specific gravity. Long before the next meal the urine is back at its normal concentration and there remains no evidence of the excess burden that was recently put on it. The damaged kidney must take a much longer time to rid the body of the surplus and the resulting urinary picture shows only slight increase of sodium chloride concentration and of specific gravity, but a prolonged increase of urinary volume which may last even over the period of the next meal.

The normal kidney at night is able to concentrate the urine to such an extent that the amount voided after eight or more hours in bed is about the same volume as that voided at any one time during the day. The damaged kidney on the contrary excretes at night increased volume of a lower specific gravity. This accounts for the nocturia.

First in point of time, then, there develops fixation of volume and of specific gravity with increase in the night volume, next fixation of salt excretion with approximately the same amount excreted in every two-hour period, and still later, fixation of total nitrogen excretion. The kidneys retain their ability to concentrate nitrogenous excretory products longer than they do the capability of concentrating sodium chloride. As the renal damage progresses the kidneys come to behave less and less like a functionating glandular organ and more and more like a mechanical filter.

The two-hour renal test as adapted to use in private practice may be outlined as follows:

(A) Direct the patient to eat on the two days preceding the collection of the urine as well as the day of the test ordinary meals such as are served in the average American household.

(B) On the day of the meal he is to take an excess of salt at the noon meal. He should distribute a level teaspoonful in his food in whatever manner his tastes may dictate.

(C) The patient's fluid intake should be that to which he has been accustomed in his daily life fairly evenly distributed over the day.

(D) At 7 A. M. of the day of the test he should void and discard the urine. Then every two hours, beginning at 9 o'clock, he should void and the individual collections should be kept separately in a cool place. The collection from 9 P. M. until 7 A. M. should be made in one container. As far as the patient is concerned his part of the experiment is completed when he has voided at 7 A. M. into the night specimen.

(E) After all of the specimens have been collected volume and specific

gravity of each should be noted. Determination of salt content and total nitrogen content require considerable special apparatus. Since variations from the normal in the manner of their excretion occur only after fixation of volume and of specific gravity has taken place, determination of the condition of the two latter is entirely sufficient for diagnostic purposes. Normally the specific gravity should at times be above 1018, particularly after meals. With the specific gravity constantly below 1018 there is present "fixation of specific gravity." There should be some definite variation of urinary volume among the two-hour specimens. The night specimen (including both the collections of 9 P. M. and 7 A. M.) should not measure over 400 c.c. volume. Its specific gravity should be 1018 or above.

(6) *Phenolsulphonephthalein Test.*—The technic of this test as originally described is capable of considerable simplification without disqualifying alteration of the end result. Two hours are required for the completion of the test. The apparatus necessary consists of one hypodermic syringe, a needle for intramuscular injection, ten or twelve tubes of practically constant diameter, a 1000 c.c. graduate, 40 per cent sodium hydroxide solution and the reagent phenolsulphonephthalein. This reagent may be obtained from several manufacturers put up in sterile 1 c.c. ampules. The contents of one ampule is to be injected.

The patient is directed to void. This urine is saved. One c.c. of the dye phenolsulphonephthalein is injected intramuscularly either into the deltoid muscle (care being taken not to injure the periosteum of the humerus) or into the gluteal muscles. The patient now drinks 200 c.c. (one glass full) of water. At the end of one hour he is to drink 200 c.c. more water and two hours from the time that the injection was made the patient again voids. This second urine specimen is to be examined to determine what per cent of the "phthalein" has been excreted during the period. Normally about 60 per cent should be present in the urine. A return of 40 per cent or less indicates a moderately advanced nephritis. The severity of the disease is greater as the amount of dye returned is less and less. An excretion of less than 10 per cent in the two-hour interval indicates severe renal damage and calls for a guarded prognosis. Usually at this stage it is a question of months or less, although exceptional cases, under careful treatment, have been known to live six or eight months with kidneys so diseased as to excrete practically none of the "phthalein" in the period.

In one condition other than nephritis the excretion of phenolsulphonephthalein may be reduced, namely, in chronic passive congestion of the kidneys such as develops in cardiac decompensation. Here the appearance of the dye in the urine may be delayed and unless this factor is taken into account the decrease in total two-hour output may be exaggerated.

An excretion of large amounts of the dye (80 per cent in two hours) indicates a hyperpermeable or better, hyperirritable, condition and is sometimes found in acute nephritis and in the early stages of chronic nephritis following the acute form. As chronic nephritis progresses the curve of "phthalein" excretion first rises and then falls and at one stage during the fall reaches 60 per

cent excretion. If one should happen to do the test only at this stage of the disease he would erroneously conclude that the renal function was normal. It is here that the two-hour renal test would provide the needed additional information. Not every case of acute nephritis is accompanied by this hypersecretion of dye. In some cases the excretion is very low and will be found to improve along with improvement in the disease itself. An excretion as high as 80 per cent in two hours will occur occasionally in normal individuals.

To determine the per cent of dye excreted the urine voided at the end of the two-hour period is placed in a 1000 c.c. graduate and measured. There should be present not less than 50 c.c. If there is less than this amount the results are untrustworthy since the subnormal excretion of water usually has an accompanying reduced excretion of the dye. The urine is next rendered strongly alkaline with concentrated sodium hydroxide solution. The white solution, or solution B, used in the determination of Fehling's test, may be substituted for the sodium hydroxide. Five or ten c.c. of the alkali are usually sufficient. It may be added until the resulting redness of the fluid ceases to increase in intensity. The urine is now diluted with water up to 1000 c.c. and thoroughly mixed. A specimen of this diluted urine is now taken and compared against a standard specimen in a graduated colorimeter and the reading directly obtained in per cent of dye. The colorimeters used are expensive and since the war began difficult to obtain. They are not essential. A satisfactory colorimeter consists of test tubes containing 10 per cent, 20 per cent, 30 per cent, etc., up to 90 per cent concentration of the dye. These are set up in a rack with just enough space between them for the insertion of a similar test tube containing the diluted alkaline urine. The color of this fluid is matched against the fluids in the series of tubes and it is not difficult to determine between which two tubes the urine tube should be placed. This colorimeter is accurate to within 5 per cent. For example, if the urine contains between 40 per cent and 50 per cent of the dye 45 per cent will be accurate within this limit. The colorimeter should be made up fresh at frequent intervals and readings are more easily made if the patient's own urine is used in the standard. This will insure there being about the same admixture of amber hue in both the standard and the urine to be tested, and it is for this reason that the urine passed at the beginning of the test is saved. To this urine when put in the liter graduate add exactly 1 c.c. of phenolsulphonephthalein, add alkali and make up to one liter. In the first tube put 1 c.c. of the diluted fluid and add 9 c.c. of water. This is the 10 per cent standard. Into the second pour 2 c.c. of the fluid and 8 c.c. of water, making the 20 per cent standard. Continue this up to the 90 per cent standard. Upon prolonged exposure to light the dye becomes less intense so for this reason it should be kept in the dark and the standard should be made fresh every time.

(7) *Ambard Test, McLean's Index of Urea Excretion and Blood Urea Nitrogen Content.*—The determination of these points requires both considerable experience and expensive apparatus. Here the amounts of urea nitrogen in the circulating blood and in the urine are determined, and at the same time

the rapidity and effectiveness of its excretion from the blood into the urine is expressed in terms of a coefficient or index of urea excretion. This corresponds quite accurately in nearly all cases to the per cent of phenolsulphonephthalein excretion. The latter is a much simpler test, has fewer sources of possible error and gives as much information. The particular advantage of the former is that we are determining the excretion of the actual substance in which we are interested, urea nitrogen, whereas in the other case we but determine the excretion of an inert dye and conclude that the excretion of urea and other waste products proceeds in a similar manner. The determination of blood urea nitrogen is important in cases of nephritis with impending uremia and should be made when possible but it is too technical and complicated to be successfully accomplished by any other than the trained laboratory man.

(8) *Therapeutic Test.*—One additional test should be described as being of value in enabling the physician to distinguish between the edema of acute nephritis and generalized edema of other origin. It occasionally happens that one is uncertain whether the anasarca in a certain case is the result of acute nephritis or cardiac decompensation from chronic myocarditis or other cardiac derangement, or whether the patient presents a combination of both diseases. Cases of mediastinal tumor or even of cirrhosis of the liver will on rare occasions present a distribution of the edema much more suggestive of nephritis than of the actual disease present.

These patients are bedridden and will presumably have been placed on a low salt diet with very limited fluid intake. A very satisfactory diet to rid a patient of general edema is the Karrell diet which consists of 800 c.c. of milk during the twenty-four hours, given in four portions at four hour intervals. The patient receives no other food or liquid. If while the patient is on this diet he does not rapidly excrete the excess water in his tissues, the question as to whether or not this failure can be due to the presence of an acute nephritis may be settled by the administration of divided doses of theocine. This drug which like caffeine appears to act directly on the kidney as a powerful diuretic will as a rule cause a profuse diuresis in all the above diseases with the exception of acute nephritis and in this latter condition the fluid excretion may even decrease. Stimulation of the damaged renal parenchyma does not improve the kidney function. As a corollary it should be inserted that diuretics in the routine treatment of acute nephritis should be discredited. Before the drug is administered the patient should have been resting in bed and have been on a low fluid intake such as the Karrell diet for at least four or five days in order that an equilibrium of intake and output may have been established.

Christian recommends the giving of approximately five grain doses three times in one day at 6 A. M., 10 A. M., and 2 P. M. The resulting diuresis may cover a period of two days or more. The drug should not be repeated for several days. There often appears to be a tendency towards slight depression of the excretory function for a day or two following this diuresis. Theocine, theocine sodium benzoate or the newer preparation, theophyllin, may be used in the performance of this test.

## DISCUSSION

By the use of the above described procedures one is now able to not only make the positive diagnosis of nephritis but also to ascertain to what stage the disease process has advanced.

The theocine test is of importance in acute nephritis. At this time salt excretion is greatly reduced. The phenolsulphonephthalein test may show a lowered excretion or an increased excretion through the hyperirritable renal cells. As the condition becomes chronic the "phthalein" excretion tends to fall as does the McLean index of urea excretion and there develops a fixation of volume and of specific gravity, followed by fixation of salt and total nitrogen excretion.

In the more marked stages of chronic nephritis we have the familiar picture with hypertension, arteriosclerosis and cardiac hypertrophy. The terminal stages bordering on uremia are evidenced by a "phthalein" excretion below 10 per cent, frequently albuminuric retinitis and a markedly increased blood total nonprotein nitrogen content. Whereas the normal is under 30 mg. per 100 c.c. of blood, in impending uremia it may rise to 60 or 100 mg. or higher.

The following table from Mosenthal and Lewis illustrates well the laboratory findings that are to be expected at the various stages of nephritis:

| DEGREE OF IMPAIRMENT OF RENAL FUNCTION | PHENOLSULPHONEPHTHALEIN PER CENT | NONPROTEIN $N_2$ OF BLOOD MG. PER 100 C.C. | UREA $N_2$ OF THE BLOOD MG. PER 100 C.C. | TEST MEAL FOR RENAL FUNCTION | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | NIGHT URINE | | VARIATIONS IN SP. GR. WHEN HIGHEST IS | | | |
| | | | | C.C. | SP. GR. | 18 | 17 – 15 | 14 – 13 | 12 |
| Normal 0 | 60 + | 30 – | 15 – | 400 – | 18 + | 9 + | | | |
| Slight + | 59 – 40 | 31 – 45 | 16 – 27 | 401 – 600 | 16 – 17 | 8 – 5 | 6 + | | |
| Moderate ++ | 39 – 25 | 46 – 65 | 28 – 44 | 601 + | 15 – | 4 – | 5 – 4 | 6 + | |
| Marked +++ | 24 – 11 | 66 – 90 | 45 – 64 | ... | ... | 3 – | 5 – 4 | 6 + | |
| Maximal ++++ | 10 – 0 | 91 + | 65 + | ... | ... | ... | 3 – | 5 – | 6 + |

Hypertension and arteriosclerosis do not invariably accompany chronic nephritis. Any one of these conditions or any combination of two of them may be found in one patient. High blood pressure, unaccompanied by marked nephritis, so-called "essential hypertension," usually shows moderate renal damage as indicated by positive findings in the two-hour renal test. The other special tests may remain essentially negative. In time there is a decrease in renal efficiency but death is more liable to be from apoplectic phenomena than from uremia.

The classification of nephritis by the above described laboratory methods is functional rather than anatomical. No mention has been made of chronic interstitial nephritis as contrasted with the chronic parenchymatous variety. We are not so much interested in whether it is the glomeruli or the tubules that are damaged as we are in whether the kidneys may satisfactorily care for the body waste. Recent investigations have shown that if one contents himself with the finding of "chronic nephritis" he will be correct far oftener than if he endeavors to elaborate upon this diagnosis. At a time when pathologists are still disputing among themselves concerning the character of renal lesions found at autopsy, it is well for the internist not to endeavor from examination of the living subject to describe the location of the lesion in the kidneys themselves.

# THREE CASES OF PARIETAL AORTIC THROMBOSIS*

By Paul G. Woolley, M.D., Cincinnati, Ohio.

THE following cases are of interest because the symptoms were associated with, and perhaps largely the results of, partial, i. e., incomplete aortic thrombosis. Two were patients on the neurologic service; one was on the medical service. All were evidently luetic. In one, the central nervous symptoms were acute; in the others, chronic. One patient was an old man. Two were young.

## CASE I

G. B., Hospital No. B-1578, a white man aged 35, was admitted to the Cincinnati General Hospital on March 2, 1917, in a somewhat maniacal condition. He would not respond to questions and talked irrelevantly and foolishly. The following history was obtained from his physician:

An uncle of the patient had had an acute maniacal attack, similar to that of this nephew, at the age of 40. During this attack he was sent to an asylum where he died later. A daughter of this uncle—a cousin of the patient—also developed acute mania, at the age of 35, and was committed to an asylum where she now is. A father of this uncle was also confined in an asylum. The history of his condition is not known. For at least two weeks prior to the present outbreak, the patient had been apparently perfectly normal mentally. At the time of the attack, which took place in a store, the patient's pupils were not fixed, and so far as the doctor knows they have never been fixed before.

The following history was obtained from a friend: On Tuesday, Feb. 28, 1917, the patient was working as usual in a grocery store when suddenly, it was noticed, he could not speak. He stepped away from the counter in a dazed way and proceeded to leave the store. His employer called to him but he continued his course. The employer then ran after him and with great difficulty brought him back fighting and incoherently mumbling. Upon reaching the store the patient had four convulsions in rapid succession. These began in both arms, and involved the entire body. The mouth opened and closed. The tongue would have been bitten if a piece of wood had not been inserted between the teeth. There was no cry. The convulsions seemed to be bilateral. Each convulsion lasted from 1 to 2 minutes, and after they had disappeared the patient remained stuporous for some time. On Wednesday the condition seemed to be unchanged. On Thursday he began to talk at random, foolishly and incoherently. On Friday he was brought to the hospital. The patient has been married a year. His wife is five months pregnant. He is not a drinker. An uncle thinks that he uses no alcohol.

*Present State.*—The patient is a poorly nourished, poorly developed white man aged about 35 years who refuses to cooperate in his examination. He can not be drawn easily into conversation. His memory can not be estimated for he refuses to respond to questions. When a question is put to him he grins foolishly, stutters and usually says something containing the letters p and t, and the figures 2, 1, and 10. The sentences are absolutely meaningless. He seems to see and hear normally but this is not secure. The right pupil is slightly larger than the left. Both react slightly to strong light. The reaction to accommodation could not be determined because of lack of cooperation. The patient opens his mouth mesially. He does not flinch when the face is forcibly pricked with a pin. There is no facial asymmetry and the facial movements seem normal. There is decided stumbling speech, stuttering, and syllable skipping. The pulse is normal. The patient refuses to protrude the tongue which lies quietly in the median line in the mouth. There is evidently sensory disturbance for pain. The patient does not flinch when pricked with a pin. There is no corporeal asymmetry and no evident loss of power. There are no contractures, tremors or spasms. The knee jerks, arm jerks, and periosteal reflexes are ex-

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aggerated. The abdominal and cremasteric reflexes are absent. There is no clonus, and no Babinsky. The gait is normal.

During the night of March 4th, the patient became very noisy. No tremor developed. The temperature rose suddenly to 103° and the pulse to 112. The patient was forcibly restrained and fought all day long at the shackles and restraining sheet. At four o'clock P.M., he was given Hogan's solution intravenously. This quieted him for about 2 hours. He then became violent again. On the following day the temperature was 104, the pulse 116. All day he was wildly delirious and fighting his restraint. He was tremorous, and muttered continually to himself. The pupils were wide, equal and did not respond to light. During the following day the condition remained the same—noisy, muttering, delirium with high temperature. There was no rigidity or retraction of the neck. The next day he was pulseless but constantly delirious and muttering. The pupils remained dilated and fixed.

Death occured at 10 A.M., on March 9, 1917.

The urine on March 5th was milky, yellow, cloudy and acid. It contained a trace of albumen but no sugar or casts.

*Clinical Diagnosis.*—Acute paresis, acute diffuse nephritis.

Fig. 1.—Case B. 1578. Note the pedunculated thrombus attached to the aortic wall.

AUTOPSY PROTOCOL

The body was that of a fairly well built, rather slender man of not more than 30 years of age. There was a very slight edema of the ankles. Rigor mortis was not present. Postmortem lividity was faint. Over the wrists and elbows were superficial excoriations and over the sacrum, there were recent, shallow, somewhat inflamed, slightly ulcerated excoriations. The pupils were dilated, the left slightly more than the right. The left foot, extending about 1 or 2 inches above the ankle, was cyanotic. The finger nails were pale. Over the thorax and in the hypochondriac region on the left side were a number of pale greenish bruises.

The brain weighed 1410 grams, was markedly congested and tremendously edematous, dripping fluid. The dura was not abnormally adherent. The pia was thickened and opaque, particularly over the frontal aspect of the brain. There was a definite atrophy of the frontal convolutions with flattening and widening of the sulci. Upon palpation the brain seemed to be more sclerotic than usual. This was more apparent on the right side. The vessels were not sclerotic. The brain was preserved in formalin for further study. In the spinal dural canal there was a considerable increase of perfectly clear limpid fluid. The subcutaneous tissues were well developed. The muscles were fairly well developed, dark in color and dry. The lower margin of the liver was 4.5 cm. below the tip of the ensiform and at the costal margin in the right mammillary line. The urinary bladder was distended

with urine. The intestines were small and congested, but there was no evidence of inflammatory change. The appendix was *in situ*. The omentum was coiled up along the transverse colon.

When the sternum was removed, the lungs collapsed partially. In the left pleural cavity was one small band of adhesions posteriorly at the upper part of the lower lobe. The right lung was completely free. There were no adhesions between the lobes. There was a very small amount of anthracosis. Both lungs appeared, grossly, completely healthy. In the left main bronchus was a small amount of thick greenish pus. There was a small amount of thymus remains. The mesentery was well supplied with fat and slightly edematous.

The right kidney was soft, pale, succulent, its capsule came off with ease, leaving a perfectly smooth surface. Here and there upon the surface were rectangular areas of pale yellowish material surrounded by definite zones of congestion, which resembled anemic infarcts. The cortices in each kidney were of less than normal thickness. The whole organ was rather firm, the friability decreased, the line of demarkation between cortex and medulla rather faint. There was an increased amount of perirenal fat and the pelves were healthy. The left kidney resembled the right.

The spleen was small and rather flabby, except at one area where there was a large infarct, mottled in character, measuring 4 cm. at its greatest depth and 3.5 cm. wide.

The heart was small, somewhat dilated and flabby. On the right side it was contracted, and firm on the left. There were no auricular thrombi in the right auricle. There were no pulmonary or tricuspid lesions. There were no thrombi in the left auricle or auricular appendage. The mitral orifice permitted the passage of two fingers. The mitral leaflets were somewhat edematous but otherwise not abnormal. The aortic valves were perfectly healthy apparently except for a few adhesions at their points of connection, but just 1 cm. above the junction between the right and posterior aortic cusps, in a hyaline hyperplastic area which seemed to be of luetic origin, was a small ulcerated surface covered with a small amount of thrombus. Lying free in the aorta just above this was a piece of thrombus that measured 2.5x1.5x1 cm., which was firm, pale and evidently cavitated. In the transverse arch just external to the mouth of the subclavian was another area similar in every respect to that above the aortic valve to which was attached a long pedunculated, white, fibrinous thrombus. There was comparatively little change in the aorta aside from some indistinct puckering which was most marked in the transverse arch and a considerable amount of fatty degeneration which extended throughout the aorta.

The left lung was apparently perfectly healthy except for one small patch of fibrosis and calcification immediately beneath the adhesions. The right apex was scarred. There were also a few old adhesions between the middle and upper and lower lobes. Just at the apex of the lower lobe there were some patches of congestion with some evident consolidation beneath them. On the pleura there was no exudate. In the lower part of the lower lobe there were several other similar areas and posteriorly there were a few more that resembled these upper ones. Over none of these was there any exudate. In some of the bronchi there were small amounts of yellowish mucous purulent material. These areas of congestion in this lobe were apparently areas of inflammatory edema. There was a larger posterior one which seemed to be a very recent infarct for in the vessel supplying it a thrombus was found.

The liver was almost completely healthy externally except for the presence of a few capsular linear markings. On section, the organ showed some patchy fatty change and some moderate congestion. The gall bladder was filled with a brownish thick mucoid bile. There were no calculi present. Except for some patchy ecchymoses in the ileum there seemed to be no lesions in the intestines.

The stomach was small and contained a small amount of bile-stained fluid. There was nothing abnormal in the stomach or duodenum. The pancreas was healthy.

*Anatomic Diagnosis.*—Luetic mesaortitis; aortic mural thrombosis; renal, pulmonic, and splenic infarcts; chronic diffuse nephritis; obsolescent pulmonary tuberculosis; purulent bronchitis; edema of the brain.

## REMARKS

It is our opinion that the acute nervous symptoms in this case were immediately due to numerous small cerebral emboli which reached the brain by way

of the carotids from the thrombus in the aorta. At least, it were better to say, we feel that these symptoms may have been due to such a phenomenon. There was no macroscopic evidence of cerebral embolism. How much influence the abnormal mental background had in the picture—in the production of a susceptibility to trauma—can be only guessed. There can be no doubt about the background. There is also anatomic evidence that the brain as a whole was not a normal one. Sections of the cerebral cortex showed perivascular infiltrations and edema, and round-cell infiltrations of the pia,—evidences of paresis. Sections of the cord showed no suggestive changes. (W. E. Kiely.)

CASE II

C. S., Hospital No. B-1043, a white man 61 years old, was admitted to the Cincinnati General Hospital on Feb. 12, 1917, in a semiconscious condition. He attempted to answer questions but was unintelligible. When asked to protrude the tongue he responded. The

Fig. 2.—Case P. 1043. The aortic arch (x), from the outside showing the dilated innominate artery with its parietal thrombus propagated for the aorta, and to the right of this vessel, the completely blocked carotid. The wide opening above the innominate is the trachea.

tongue deviated to the right. He was unable to hold up the right arm or move the right leg. He was able to move the left arm and leg. The pupils reacted to light, and the left pupil seemed smaller. The arm jerks were about equal, though possibly the left was greater. The abdominal and cremasteric reflexes were present on the left; absent on the right. The knee jerk was diminished on the right; exaggerated on the left. There was no ankle clonus. On the right the Babinski sign was present; on the left it was absent. When the sole of the right foot is tickled the patient draws the leg up weakly. The heart sounds were clear, and there were no murmurs. The patient appeared drowsy and yawned frequently.

From a niece it was learned that the patient had not been working for about 3 years, but has seemed well until the time of the present attack which began while he was riding on a street car. A neighbor who was in the same car helped him off, and with difficulty got him home. No accurate description of the attack was obtained although it was determined that there were no convulsions.

On Feb. 15, a slight ankle clonus appeared on the right, though the general condition of the patient remained about the same.

On Feb. 25, the patient was slowly sinking, and on March 11, he died.

During the hospital period, the patient's's pulse ran from 88 to 134; the temperature from 97° to 101°; and the respirations from 20 to 24.

*Clinical Diagnosis.*—Cerebral hemorrhage; lues.

AUTOPSY PROTOCOL

The body was that of a well-built, fairly well-nourished man of about 55 years of age; rigor mortis and lividity were present. There was no edema of the ankles. The finger nails were somewhat cyanotic. The eyelids were glued together with a purulent secretion. The pupils were equal, neither dilated nor contracted. Just external to the right eye was a focal dermatitis with some suppuration. On either side of the neck beneath the ears, were areas of cutaneous hyperplasia, larger on the left, which in some way resembled nevi, and were covered with hair. The edges were rather sharp, however, although not regular. The skin over them was thickened; and, extending from the posterior margin on either side, there were excoriated areas which measured not over ½ cm. in diameter, in which there were distinct evidences of inflammation. These smaller patches resembled the patches to the right of the right eye. The peripheral lymph glands were not appreciably enlarged. The teeth were in rather bad condition; the gums were quite pyorrheic. There was one gold crown and several fillings in the upper teeth. The subcutaneous tissues were very well developed; the muscles were only fairly well developed but of good color. The omentum was thickly filled with fat and was partly coiled up above the transverse colon and stomach. The appendix was present. There was no obvious lesion in the abdominal cavity except a few old adhesions between the gall bladder and hepatic flexure of the colon and rather numerous old adhesions about the spleen. The lower border of the liver was 5.5 cm. below the ensiform and 3 cm. above the costal margin in the right mammillary line.

The brain was exceedingly edematous and the veins were all deeply congested. The pia contained so much fluid that it appeared gelatinous. Externally there was no evidence of any arteriosclerosis and there was no evidence of superficial inflammation. On section of the brain it was found that the ventricles were slightly dilated and throughout the substance of the brain on both sides the smaller vessels were congested. On the left side it appeared that almost the whole thalmic region and some of the surrounding white matter was generally destroyed. The degenerated softened tissue was for the most part almost white, although in some areas there was a tinge of yellow. The appearances suggested that there was a certain amount of suppuration present.

When the sternum was removed, the lungs did not collapse. In the left pleural cavity was one group of old lateral adhesions over the lower lobe and some old diaphragmatic ones. In the right pleural cavity there was an obliteration of about half the cavity. There was no increase of pericardial fluid. The mesentery was very well supplied with fat. The spleen was completely buried in old fibrous adhesions so that it was firmly adherent to the stomach, liver and diaphragm. There was a large increase of perirenal fat. The adrenals were cavitated.

The right kidney was small, pale, flabby, and decidedly edematous. The capsule removed with only slight difficulty and left a fairly smooth surface. The capsule, however, separated, showing a very finely granular surface. At one place was a scarred area that resembled an infarct scar. The capsule was somewhat thin but gray. The glomeruli were not visible. The line of demarkation between cortex and medulla was faint. The stellate veins were somewhat injected. The pelvis was healthy. The left kidney resembled the right in all respects except for the presence of the scar. The blood vessels of the kidney were somewhat patulous.

The heart was large and flabby and, particularly on the right, dilated. The coronary vessels were not tortuous and not evidently sclerotic. In the right auricle was a large agonal clot. There was no lesion of the tricuspid or pulmonary valves. There were no thrombi in the left auricle. On the mitral valve was an adherent clot and the edges of the mitral leaflets were somewhat thickened. The clot upon the mitral valve was evidently one of not very long standing (agonal) and at the point of attachment on the valve there was no lesion. The aortic leaflets were healthy except that at the point of attachments there was a certain amount of sclerosis. The aorta itself was tremendously and diffusely damaged by an atherosclerotic process which had led to subintimal hyperplasia, thickening, wrinkling, and to the presence of atheromatous ulcers, and abscesses together with calcification. Just at the apex of the arch there was a large clot that was adherent to an ulcerated placque just at the opening of the innominate artery which was considerably

dilated. This clot extended from the opening of the innominate to the origin of the carotid which was completely blocked for some distance by a mixed lamellated thrombus. The aorta, throughout its thoracic portion, was considerably dilated, and just in the region of the innominate the dilatation was more distinct and acquired a saccular form. It was from the apex of this saccular secondary aneurism that the dilated innominate originated. The myocardium was flabby and for the most part pale, but particularly in the papillary muscles, there were zones of deep congestion alternating with areas that were paler, somewhat yellow, indicating some deposition of fat. The mural endocardium was almost generally thickened. The coronary openings were patent.

The left lung was crepitant throughout, contained no areas of consolidation and was merely mildly congested. The right lung presented the same appearances. The spleen, thickly covered with the remains of old adhesions, was exceedingly soft. The malpighian follicles were visible as small points. The substance had no increase in connective tissue, was almost diffluent and of a brownish-red color. The liver was large and flabby. The surface had a couple of grooves across the dome on the right. The whole organ was flabby. Section of the parenchyma showed a mottling due to some moderate degree of passive congestion evidently, with slight central lobular atrophy. The whole organ was edematous. In the left lobe the evidences of passive congestion were more brilliant. Aside from the moderate increase in mucus, the stomach and duodenum showed nothing unusual. The pancreas was slightly congested and, particularly in the tail, there seemed to be some areas of parenchymatous hypertrophy, in evidence of which were islands of very pale firm tissue. There was very little splanchnic arteriosclerosis.

*Anatomic Diagnosis.*—Luetic mesaortitis; dilatation of the aortic arch; aneurism of the aortic arch including the innominate artery; aortic mural thrombosis; thrombosis of the left carotid artery; cerebral embolism; edema of the brain and meninges; chronic diffuse nephritis; myocardial degeneration; hypertrophy and dilatation of the heart; pyorrhea alveolaris.

### REMARKS

In this case, there can be no doubt of the immediate cause of the symptoms. They were due to cerebral embolism. If, in the former case there were very small emboli, in this case they were large and produced focal lesions that were easily discovered.

### CASE III

E. M., Hospital No. A-3062, a negro 23 years old, was brought into the receiving ward of the Cincinnati General Hospital, on May 1, 1916.

No history could be obtained. All that could be learned was that he had come from a neighboring town two days before. On admission, his temperature was 102°; pulse 104; respirations 40.

The patient is a powerfully developed man. He is lying on his back and can not be roused. His respirations are deep and irregular. The pupils are pinpoint in size and equal. They fail to respond to stimuli. On the right malar prominence there is a superficial abrasion but no swelling. There is no swelling of the face. There is no stiffness of the neck. The left angle of the mouth is pulled slightly outward and there is an occasional twitching of the muscles in this region. The neck is negative. The thorax is well formed and symmetrical. Expansion is equal but rather small. The lungs are clear throughout on auscultation and percussion.

The point of maximum cardiac impulse is 9.5 cm. to the left of the midsternal line in the fifth interspace. The impulse is rather diffuse and fairly strong. The relative cardiac dullness extends 10.5 cm. to the left of the midsternal line, and 6.5 cm. to the right. There is no retrosternal dullness. Both sounds are strong and forcible at the apex, but not so strong at the base. On auscultation there is a faint systolic murmur heard at the apex, but louder at the left border of the sternum in the third and fourth interspaces. It is not transmitted beyond this region. The pulse is regular in force and rhythm. The blood pressure is 160 systolic, 94 diastolic; pulse pressure 66.

The abdomen is just below the level of the ribs and is symmetrical. There is no rigidity or tenderness. The liver and spleen are not enlarged.

The abdominal and cremasteric reflexes are absent. Knee jerks are not obtained. Plantar stimulation elicits a very slight plantar flexion of the great toe. Oppenheimer's reflex is absent. There is no clonus. There is no spasticity of the upper or lower extremities.

The urine obtained in the receiving ward contained a considerable amount of albumin. A specimen obtained by catheterization the following morning contained a small amount of albumin, no sugar, acetone, or diacetic acid, and coarsely granular casts.

Blood examination gave 4,500,000 red cells; 8,600 leucocytes, and 80 per cent hemoglobin. A differential count gave 23 per cent lymphocytes, 12 per cent mononuclears, 4 per cent transitionals, 61 per cent neutrophils, no eosinophils, or mast cells. The urea content of the blood was 100 mg. The hydrogen-ion concentration was 7.65.

Shortly after admission 350 c.c. of blood were withdrawn at the elbow, after which the systolic pressure dropped from 160 to 138, without change in the diastolic. An intravenous injection of a liter of Fischer's solution was given after venesection and following this the blood pressure rose to 180 systolic, and 100 diastolic.

Spinal puncture was done and about 50 c.c. of fluid was removed, apparently under no increased pressure. The fluid was blood-tinged. Immediately after this the patient roused sufficiently to give his name and age. There was no change in the pupillary reaction, and he soon relapsed into coma. The following day spinal puncture was repeated, and the fluid obtained was not under any increased pressure. There was a small amount of blood in each of the four tubes in which the fluid was collected. A spinal Wassermann was negative; a blood Wassermann was strongly positive.

Fig. 3.—Case A. 3062. Central infarction (embolism).

The patient's condition remained unchanged throughout the day. At 6:30 P.M. the temperature rose to 106.6°; the respirations became labored; the pulse was fair. The pupils became extremely dilated and fixed. Ophthalmoscopic examination showed nothing unusual. The blood pressure was 130 systolic, 100 diastolic.

The patient died at 7 P.M., on May 2, 1917.

*Clinical Summary.*—A colored man, 23 years old, was admitted in coma. He was well developed, the pupils were equal and pinpoint. The reflexes were abolished. The heart was dilated and a systolic murmur was heard at the apex, transmitted toward the base, with its maximum intensity in the 3rd and 4th interspaces near the sternum. The blood pressure on admission was 160 systolic and 94 diastolic. The eyegrounds were negative on ophthalmoscopic examination. The urine contained some albumin and coarsely granular casts. The blood urea was 103 milligrams. The spinal fluid contained red blood cells.

*Clinical Diagnosis.*—Pachymeningitis interna hemorrhagica; chronic nephritis; chronic myocarditis; hypertrophy and dilatation of the heart.

DISCUSSION (R. S. M.)

The lack of a history is unfortunate. There could be found no evidence of trouble sufficient to cause the present condition and no evidence of poisoning could be found. The urinary findings were against acute nephritis, although the secretion of urine during the last day of the patient's illness was much diminished. The increase of the blood

urea points to renal insufficiency. The blood pressure was moderately elevated. The spinal fluid on two occasions contained blood which apparently did not come from the puncture wound, as it was uniform in all parts of each specimen. There were no focal nervous symptoms. The absence of these, together with the presence of blood in the spinal fluid and the moderate elevation of blood pressure led us to suspect pachymeningitis hemorrhagica interna. In a process as acute as this, the absence of focal symptoms, if this diagnosis were correct, would be somewhat puzzling. Uremia seemed probable from the increase of urea, the scanty secretion of urine and the elevation of blood pressure. The absence of changes in the eyegrounds, however, is noteworthy.

AUTOPSY PROTOCOL.

The body was that of an exceedingly well-built, well-nourished, colored man, probably 35 years of age. Rigor mortis was present, posterior lividity was also present, but not brilliant. Over the right malar region was an excoriation. The pupils were equal. The teeth were in fairly good condition, but all of them showed atrophy of the crowns. There was no pyorrhea. The finger nails were pale. In the bend of both arms were surgical wounds closed with silkworm-gut sutures. The subcutaneous fat was exceedingly well developed. The muscles were exceedingly well developed, of good color and dry. The omentum formed an apron over the anterior surface of the intestines and was well supplied with fat. The small intestine was for the most part contracted and the large intestine was dilated, chiefly with gas. The appendix was *in situ*, and apparently healthy. There was no abnormality of appearance or arrangement of the intestines. The lower border of the liver lay 5 cm. below the ensiform. There were many old veil-like adhesions between the anterior surface of the liver and diaphragm. When the sternum was removed, the lungs did not collapse. In the left pleural cavity there was no increase of fluid and no adhesions except between the surface of the lower lobe and diaphragm. There were no adhesions and no increase in fluid in the right pleural cavity. There was no abnormal increase in fluid in the pericardial cavity. The bronchial lymph glands contained old obsolescent tubercles.

The heart was excessively increased in size, the right side somewhat dilated and evidently slightly hypertrophic. The tricuspid and pulmonary valves showed very little change. The mitral seemed to be approximately perfectly healthy. The aortic leaflets showed a few adhesions at their points of insertion and the right one was fenestrated at its margin. Beginning above the aortic valves, there was very distinct syphilitic aortitis and about half way between the valves and the origins of the great vessels of the neck were several mural vegetations, one of them being 3.5 cm. in length by 1 cm. in width, the others being smaller. Also, in the thoracic aorta, just above the diaphragm there was another mural thrombus which measured 2 by 1.5 cm. in width. All of these were about 0.5 cm. thick.

The liver was of fair size, the capsule was irregularly thickened and upon it were numerous scars of old adhesions. The whole external surface was pale. On cross section, the parenchyma appeared to be cloudy, with here and there rather discrete areas of fatty degeneration. There was evidence of a certain degree of passive congestion, not, however, distinctly chronic. The gall bladder was filled with a yellowish-brown, rather thick, mucoid bile and contained no calculi.

The right lung was somewhat voluminous and rather bluish-purple in color, and crepitant throughout except for a single area 1.5 cm. in diameter, just beneath the middle of the lateral surface of the lower lobe. There was no sign of pleuritis. On section, the area of consolidation appeared to be an obsolescent fibroid tubercle with caseous center. The lung tissue was saturated with fluid and exceedingly congested. The left lung resembled the right. There were no areas of consolidation to be felt. The whole lung seemed to be somewhat more boggy than the right. On section, the same condition of intense congestion and edema was present. From some of the smaller bronchi, yellowish drops of pus were expressed and upon the cut surface of the lower lobe, one could feel and see very small areas of consolidation not over 1 or 2 mm. in diameter, which had an indistinct yellowish appearance, and pressure upon them forced out a creamy, yellowish pus. There were large numbers of these areas of consolidation throughout the lower lobe and some still smaller ones in the upper lobe. All of the finer bronchi contained pus. The bronchi were all intensely congested but evidently only in the smaller ones was there any purulent exudate.

The spleen was small and the surface was scarred with the tags of old adhesions. On cross section, the pulp was firm, congested and the malpighian bodies were easily

visible as discrete points. There were the healed remains of old tubercles. There was no evidence of increased fibrous tissue in the organ. The pancreas was exceedingly soft and evidently was undergoing autolysis. The stomach and intestines showed very well marked postmortem changes. In addition to this, the stomach showed some morocco-leather appearance. The duodenum showed nothing unusual. There was no evidence of passive congestion. There was nothing unusual in the intestinal tract. The mesentery was quite fatty. The mesenteric lymph glands were not evidently enlarged. All of the abdominal organs, superficially at least, were exceedingly dry. The spleen was surrounded by old adhesions, some of which were between it and the stomach. Neither adrenal showed anything macroscopically unusual.

Over the lower pole of the right kidney, the fatty capsule was infiltrated and more than usually adherent. The capsule removed with ease leaving a smooth surface which, as a rule, was pale, but was irregularly mottled with areas of hemorrhage, so that it had, particularly in the lower half, an appearance of marble. On section, it appeared that except for about a fourth of the parenchyma, the kidney was the seat of multiple infarctions. The left kidney was exceedingly large, like the right, and on section showed practically the same series of changes. It seemed possible, from the appearances in the kidney, that some of the infarcts were older than others, and at each inferior pole the process seemed to be most recent. For the most part, these infarcts seemed to be white; the most recent ones, however, were red.

"The dura was not thickened and showed no unusual changes. The pia showed an exceeding grade of congestion with, however, very little edema. The brain was rather dry. In the superior longitudinal sinus, just over the occipital lobes, was a definite, adherent, gray, friable thrombus. The convolutions were flattened and there was no accumulation of fluid between them. There was evidently no arteriosclerosis. Particularly the internal aspects and, to a certain extent, the external, ventricular, and inferior aspects of the occipital lobes were intensely and generally congested. All of the brain substance in these areas was evidently saturated with blood pigment and the areas that showed these hemorrhagic changes seemed to be softer than the rest of the brain. The whole appearance suggested red infarction. Examination of the brain after it had been hardened, revealed a large infarct on the inferior surfaces of the occipital lobes extending up through the cortex and about 1 cm. into the white matter. The left infarct passed up and forward above the cortex to a point just above the left cerebral peduncle; the right infarct passed up through the oliva and ended just beneath the corpus callosum at a point just above the middle of the optic chiasm." (Note by Chas. E. Kiely.)

*Anatomic Diagnosis.*—Aortic mural thrombi; cerebral and renal infarcts; thrombosis of the superior longitudinal sinus; dilatation of the right heart; luetic mesaortitis; acute lobular pneumonia (bronchiolitis); healed obsolescent pulmonary and splenic tuberculosis; perihepatic and perisplenic adhesions.

## REMARKS

This case is unusual in several respects. In the first place, thrombosis of the aorta is not a common occurrence. When it does occur, it is not infrequently followed by cerebral embolism, but not to the extent shown here. Complete infarction (red softening) of both occipital lobes is exceedingly unusual.

## SUMMARY

Three cases are reported in which aortic thrombosis occurred at the seats of luetic lesions. From these thrombi, emboli were carried to various portions of the body. In one case the symptoms were acute; in one they were chronic and referred to paralytic disturbances; in one they were probably acute and paralytic. The varying distributions of the emboli from thrombi in essentially the same place in the aorta is interesting.

# *LABORATORY METHODS*

## TABLES FOR USE IN BLOOD ANALYSIS*

By Florence Hulton-Frankel, Ph.D., New York City

THE amount of calculation necessary in the laboratory of a large hospital where routine analyses are done, is considerable, and any device which minimizes this and introduces a greater degree of safety, from the standpoint of personal error, seems advisable. The following tables were compiled for use in this laboratory, but in view of the requests, from visitors from other laboratories, for copies of the tables it seemed that they might prove more generally useful if published.

Nonprotein nitrogen is determined in blood according to the method of Greenwald.[1] Five c.c. of blood are diluted in a volumetric flask to 50 c.c. with 5 per cent trichloracetic acid and allowed to stand about one-half hour and then centrifuged and filtered. Twenty c.c. of this filtrate are digested with 4 c.c. of a digestion mixture consisting of potassium and copper sulphate and sulphuric acid, till colorless and then 10 c.c. of concentrated alkali is added and the ammonia formed is distilled into 15 c.c. of 0.01 N acid containing 3 drops of methyl red. The condenser is carefully washed and the washings run into the receiver. One drop of methylene blue is added to the distillate which gives a purple color, and the excess of acid is titrated with 0.01 N alkali. This indicator is very sensitive, one drop of 0.01 N alkali at the end point changing the color from purple to a vivid grass-green. The burette containing the alkali is read and the results read directly in milligrams of nonprotein nitrogen, from the table. This eliminates the necessity for subtraction, thus avoiding another possibility of error and saving considerable time in the course of a day.

The figures for the majority of cases will fall within the limits of those in Table I. The figures in the left-hand column represent whole cubic centimeters of 0.01 N alkali used in the titration. The figures in the headings across the page represent tenths of a cubic centimeter; i. e., if the burette reads 4.5 c.c., look down the first column to the left until 4 is reached, then across the page on the same line as 4 until the figure immediately below 0.5 is reached, giving a reading of 73.5 mg. of nonprotein nitrogen per 100 c.c. of blood.

In ordinary routine analyses, closer readings than this are not necessary, however in more accurate work when necessary, where the burette is graduated in 0.1 of a cubic centimeter, the intervening figures can be easily interpolated. A few cases, as in uremia, will show figures higher than those recorded in Table I. In this event the same amount of filtrate is distilled into 10 c.c. of 0.05 N acid and titrated with 0.05 N alkali and the results read in the same way from Table II.

*From the Harriman Research Laboratory, Roosevelt Hospital, New York City.

TABLE I—NONPROTEIN NITROGEN

Take 20 c.c. filtrate for micro Kjeldahl, digest and distill into 15 c.c. $\frac{N}{100}$ acid
Figures give mg. N. per 100 c.c. blood.

ALKALI USED FOR TITRATION

| c.c. | .0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 105 | 104.3 | 103.6 | 102.9 | 102.2 | 101.5 | 100.8 | 100.1 | 99.4 | 98.7 |
| 1 | 98.0 | 97.3 | 96.6 | 95.9 | 95.2 | 94.5 | 93.8 | 93.1 | 92.4 | 91.7 |
| 2 | 91.0 | 90.3 | 89.6 | 88.9 | 88.2 | 87.5 | 86.8 | 86.1 | 85.4 | 84.7 |
| 3 | 84.0 | 83.3 | 82.6 | 81.9 | 81.2 | 80.5 | 79.8 | 79.1 | 78.4 | 77.7 |
| 4 | 77.0 | 76.3 | 75.6 | 74.9 | 74.2 | 73.5 | 72.8 | 72.1 | 71.4 | 70.7 |
| 5 | 70.0 | 69.3 | 68.6 | 67.9 | 67.2 | 66.5 | 65.8 | 65.1 | 64.4 | 63.7 |
| 6 | 63.0 | 62.3 | 61.6 | 60.9 | 60.2 | 59.5 | 58.8 | 58.1 | 57.4 | 56.7 |
| 7 | 56.0 | 55.3 | 54.6 | 53.9 | 53.2 | 52.5 | 51.8 | 51.1 | 50.4 | 49.7 |
| 8 | 49.0 | 48.3 | 47.6 | 46.9 | 46.2 | 45.5 | 44.8 | 44.1 | 43.4 | 42.7 |
| 9 | 42.0 | 41.3 | 40.6 | 39.9 | 39.2 | 38.5 | 37.8 | 37.1 | 36.4 | 35.7 |
| 10 | 35.0 | 34.3 | 33.6 | 32.9 | 32.2 | 31.5 | 30.8 | 30.1 | 29.4 | 28.7 |
| 11 | 28.0 | 27.3 | 26.6 | 25.9 | 25.2 | 24.5 | 23.8 | 23.1 | 22.4 | 21.7 |
| 12 | 21.0 | 20.3 | 19.6 | 18.9 | 18.2 | 17.5 | 16.8 | 16.1 | 15.4 | 14.7 |

TABLE II—NONPROTEIN NITROGEN

Take 20 c.c. filtrate for micro Kjeldahl, digest and distill into 10 c.c. $\frac{N}{20}$ acid.
Figures give mg. N per 100 c.c. blood.

ALKALI USED FOR TITRATION

| c.c. | .0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |
|---|---|---|---|---|---|---|---|---|---|---|
| 0 | 350 | 346.5 | 343 | 339.5 | 336 | 332.5 | 329 | 325.5 | 322 | 318.5 |
| 1 | 315 | 311.5 | 308 | 304.5 | 301 | 297.5 | 294 | 290.5 | 287 | 283.5 |
| 2 | 280 | 276.5 | 273 | 269.5 | 266 | 262.5 | 259 | 255.5 | 251 | 248.5 |
| 3 | 245 | 241.5 | 238 | 234.5 | 231 | 227.5 | 224 | 220.5 | 217 | 213.5 |
| 4 | 210 | 206.5 | 203 | 199.5 | 196 | 192.5 | 189 | 185.5 | 182 | 177.5 |
| 5 | 175 | 171.5 | 168 | 164.5 | 161 | 157.5 | 154 | 150.5 | 147 | 143.5 |
| 6 | 140 | 136.5 | 133 | 129.5 | 126 | 122.5 | 119 | 115.5 | 112 | 108.5 |

Creatinine and sugar are determined according to the Myers and Bailey[2] modification of the Benedict method—5 c.c. of blood are laked with 20 c.c. of distilled water and saturated with recrystallized picric acid. The saturation is accomplished by shaking the blood with the picric acid, in small stoppered flasks. The whole is centrifuged and filtered and 3 c.c. of the filtrate are used for sugar and the rest for creatinine, being compared in a colorimeter with standard creatinine solutions, after treatment with alkali. Setting the standard at 20 on the colorimeter and using the above method the creatinine may be read directly from the table in milligrams per 100 c.c. of blood.

The sugar determination is made according to the method mentioned and the standard used is 3 c.c. of a solution of pure glucose solution containing 200 mg. of glucose per liter of saturated picric acid. The same amount of standard in this case must be treated with alkali and heated exactly as the unknown. With the standard set at 20 the results in percentage of glucose may be read on Table IV.

TABLE III—CREATININE

| STANDARD SET AT 20 | 0.2 MG. PER 100 C.C. STANDARD | 0.4 MG. PER 100 C.C. STANDARD | 0.6 MG. PER 100 C.C. STANDARD | 2.0 MG. PER 100 C.C. STANDARD | 4.0 MG. PER 100 C.C. STANDARD |
|---|---|---|---|---|---|
| Unknown Reading | | | | | |
| 10 | 2.00 | 4.00 | 6.00 | 20 | 40 |
| 11 | 1.82 | 3.64 | 5.45 | 18.2 | 36.4 |
| 12 | 1.67 | 3.34 | 5.0 | 16.7 | 33.3 |
| 13 | 1.54 | 3.08 | 4.6 | 15.4 | 30.8 |
| 14.0 | 1.43 | 2.86 | 4.29 | 14.3 | 28.5 |
| 14.5 | 1.38 | 2.76 | 4.14 | 13.8 | 27.6 |
| 15.0 | 1.33 | 2.66 | 4.00 | 13.3 | 26.6 |
| 15.5 | 1.29 | 2.58 | 3.87 | 12.9 | 25.8 |
| 16.0 | 1.25 | 2.50 | 3.75 | 12.5 | 25.0 |
| 16.5 | 1.21 | 2.42 | 3.64 | 12.1 | 24.2 |
| 17.0 | 1.17 | 2.34 | 3.53 | 11.7 | 23.5 |
| 17.5 | 1.14 | 2.28 | 3.43 | 11.4 | 22.8 |
| 18.0 | 1.11 | 2.22 | 3.33 | 11.1 | 22.2 |
| 18.5 | 1.08 | 2.16 | 3.24 | 10.8 | 21.6 |
| 19 | 1.05 | 2.10 | 3.16 | 10.5 | 21.0 |
| 19.5 | 1.02 | 2.04 | 3.08 | 10.2 | 20.4 |
| 20 | 1.00 | 2.00 | 3.0 | 10 | 20 |
| 20.5 | 0.97 | 1.94 | 2.92 | 9.7 | 19.4 |
| 21 | 0.95 | 1.90 | 2.85 | 9.5 | 19.0 |
| 22 | 0.91 | 1.82 | 2.73 | 9.1 | 18.2 |
| 23 | 0.87 | 1.74 | 2.60 | 8.7 | 17.4 |
| 24 | 0.83 | 1.66 | 2.50 | 8.3 | 16.6 |
| 25 | 0.80 | 1.60 | 2.40 | 8.0 | 16.0 |
| 26 | 0.77 | 1.54 | 2.30 | 7.7 | 15.4 |
| 27 | 0.74 | 1.48 | 2.22 | 7.4 | 14.8 |
| 28 | 0.71 | 1.42 | 2.14 | 7.1 | 14.2 |
| 29 | 0.69 | 1.38 | 2.07 | 6.9 | 13.8 |
| 30 | 0.67 | 1.34 | 2.0 | 6.7 | 13.4 |

Urea is determined according to the method of Marshall[3] modified by Van Slyke.[4] Two c.c. of blood are diluted with water to about 10 c.c. and 25 mg. of pure urease added (about a gram of freshly ground soy bean may be used instead) and the ammonia formed aerated into 10 c.c. of 0.01 N acid. The last traces of ammonia are brought over by making the blood alkaline with 10 per cent sodium carbonate. Methyl red is placed in the acid into which the ammonia is aerated, so that it is possible to see if the 10 c.c. of 0.01 N acid can take care of all the ammonia formed. The methylene blue is added and the excess of acid titrated with 0.01 N alkali. The results in mg. per 100 c.c. are read from the table.

As was the case in the nonprotein nitrogen the urea will be very high in uremic cases, and the ammonia formed will have to be aerated into 10 c.c. of 0.05 N acid and titrated with 0.05 N alkali, and the results read on Table VI.

Uric acid is determined by a modification of Benedict's[5] method. 10 c.c. of blood are coagulated by adding them to 50 c.c. of boiling 0.01 N acetic acid, filtered and boiled down to a small volume and 15 c.c. of alumina cream added and filtered. The filtrate is concentrated to a few cubic centimeters and washed into a centrifuge tube and 20 drops of ammoniacal silver lactate added.

TABLE IV—SUGAR IN BLOOD

| STRENGTH OF STANDARD 200 MG. PER 1000 C.C. | |
|---|---|
| Colorimeter Reading | Percentage of Sugar in Blood |
| 7. | 0.286 |
| 7.5 | 0.267 |
| 8. | 0.25 |
| 8.5 | 0.235 |
| 9. | 0.222 |
| 10. | 0.202 |
| 11. | 0.182 |
| 12. | 0.167 |
| 13. | 0.154 |
| 14. | 0.143 |
| 15. | 0.133 |
| 16. | 0.125 |
| 17. | 0.117 |
| 18. | 0.111 |
| 19. | 0.105 |
| 20. | 0.10 |
| 21. | .095 |
| 22. | .091 |
| 23. | .087 |
| 24. | .083 |
| 25. | .080 |
| 26. | .077 |
| 27. | .074 |
| 28. | .071 |
| 29. | .069 |
| 30. | .067 |
| 31. | .064 |

TABLE V—UREA

| 10 C.C. ACID N/100 | 2 C.C. BLOOD. | | | | | | MG. UREA PER 100 C.C. OF BLOOD | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| c.c. | 0.0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |
| 0 | 150.0 | 148.5 | 147.0 | 145.5 | 144.0 | 142.5 | 141.0 | 139.5 | 138.0 | 136.5 |
| 1 | 135.0 | 133.5 | 132.0 | 130.5 | 129.0 | 127.5 | 126.0 | 124.5 | 123.0 | 121.5 |
| 2 | 120.0 | 118.5 | 117.0 | 115.5 | 114.0 | 112.5 | 111.0 | 109.5 | 108.0 | 106.5 |
| 3 | 105.0 | 103.5 | 102.0 | 100.5 | 99.0 | 97.5 | 96.0 | 94.5 | 93.0 | 91.5 |
| 4 | 90.0 | 88.5 | 87.0 | 85.5 | 84.0 | 82.5 | 81.0 | 79.5 | 78.0 | 76.5 |
| 5 | 75.0 | 73.5 | 72.0 | 70.5 | 69.0 | 67.5 | 66.0 | 64.5 | 63.0 | 61.5 |
| 6 | 60.0 | 58.5 | 57.0 | 55.5 | 54.0 | 52.5 | 51.0 | 49.5 | 48.0 | 46.5 |
| 7 | 45.0 | 43.5 | 42.0 | 40.5 | 39.0 | 37.5 | 36.0 | 34.5 | 33.0 | 31.5 |
| 8 | 30.0 | 28.5 | 27.0 | 25.5 | 24.0 | 22.5 | 21.0 | 19.5 | 18.0 | 16.5 |
| 9 | 15.0 | 13.5 | 12.0 | 10.5 | 9.0 | 7.5 | 6.0 | 4.5 | 3.0 | 1.5 |

TABLE VI—UREA

| 10 C.C. N/20 ACID. | 2 C.C. BLOOD. | | | | | | MG. UREA PER 100 C.C. OF BLOOD | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| c.c. | 0.0 | 0.1 | 0.2 | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 |
| 0 | 750. | 742.5 | 735.0 | 727.5 | 720. | 712.5 | 705. | 697.5 | 690. | 682.5 |
| 1 | 675. | 667.5 | 660.0 | 652.5 | 645. | 637.5 | 630. | 622.5 | 617. | 609.5 |
| 2 | 600. | 592.5 | 585.0 | 577.5 | 570. | 562.5 | 555. | 547.5 | 540. | 532.5 |
| 3 | 525. | 517.5 | 510.0 | 502.5 | 495 | 487.5 | 480. | 472.5 | 465. | 457.5 |
| 4 | 450. | 442.5 | 435.0 | 427.5 | 420. | 412.5 | 405. | 397.5 | 390. | 382.5 |
| 5 | 375. | 367.5 | 360.0 | 352.5 | 345. | 337.5 | 330. | 322.5 | 315. | 307.5 |
| 6 | 300. | 292.5 | 285.0 | 277.5 | 270. | 262.5 | 255. | 247.5 | 240. | 242.5 |
| 7 | 225. | 217.5 | 210.0 | 202.5 | 195. | 187.5 | 180. | 172.5 | 165. | 155.5 |
| 8 | 150. | 142.5 | 135.0 | 127.5 | 120. | 112.5 | 105. | 97.5 | 90. | 82.5 |
| 9 | 75. | 67.5 | 60.0 | 52.5 | 45. | 37.5 | 30. | 22.5 | 15. | 7.5 |

The precipitate formed is silver urate and is centrifuged off and dissolved in KCN and made alkaline with $Na_2CO_3$ and uric acid reagent added and diluted to a definite volume and compared in a colorimeter with a uric acid standard, a solution 5 c.c. of which gives 1 mg. of uric acid. For routine work the standard is set at 20. The colorimetric reading on the table gives milligrams of uric acid per 100 c.c.

TABLE VII—URIC ACID

| DILUTION OF UNKNOWN<br>VOLUME OF BLOOD<br>COLORIMETER READING | 25 50<br>10 20 | 50 100<br>10 20 | 25<br>20 |
|---|---|---|---|
| 10.0 | 10 | 20 | 5.0 |
| 10.5 | 9.5 | 19.0 | 4.7 |
| 11.0 | 9.1 | 18.2 | 4.5 |
| 11.5 | 8.7 | 17.4 | 4.3 |
| 12.0 | 8.3 | 16.7 | 4.1 |
| 12.5 | 8.0 | 16.0 | 4.0 |
| 13.0 | 7.7 | 15.4 | 3.8 |
| 13.5 | 7.4 | 14.8 | 3.7 |
| 14.0 | 7.1 | 14.3 | 3.5 |
| 14.5 | 6.9 | 13.8 | 3.4 |
| 15.0 | 6.7 | 13.3 | 3.3 |
| 15.5 | 6.4 | 12.9 | 3.2 |
| 16.0 | 6.2 | 12.5 | 3.1 |
| 16.5 | 6.0 | 12.1 | 3.0 |
| 17.0 | 5.87 | 11.75 | 2.9 |
| 17.5 | 5.7 | 11.4 | 2.8 |
| 18.0 | 5.55 | 11.1 | 2.75 |
| 18.5 | 5.4 | 10.8 | 2.7 |
| 19.0 | 5.2 | 10.5 | 2.6 |
| 19.5 | 5.12 | 10.25 | 2.55 |
| 20. | 5.0 | 10. | 2.5 |
| 21. | 4.7 | 9.5 | 2.3 |
| 22. | 4.5 | 9.1 | 2.2 |
| 23. | 4.3 | 8.7 | 2.1 |
| 24. | 4.1 | 8.3 | 2.05 |
| 25. | 4.0 | 8.0 | 2.0 |
| 26. | 3.8 | 7.7 | 1.9 |
| 27. | 3.7 | 7.4 | 1.85 |
| 28. | 3.6 | 7.1 | 1.8 |
| 29. | 3.4 | 6.9 | 1.7 |
| 30. | 3.3 | 6.7 | 1.6 |

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[3]Marshall, E. K., Jr.: Jour. Biol. Chem., 1913, xv, 487.
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[5]Benedict, S. R.: Jour. Biol. Chem., 1915, xxi, 61.

# TWO SUGGESTIONS OF APPARATUS FOR THE TEACHING LABORATORY*

## 1. A Device for the Determination of Time of Muscular Contraction and Relaxation. 2. An Automatic Key.

By Ardrey W. Downs, M.D., and George Hays, M.D., Montreal, Canada

THE first apparatus described in this paper (Fig. 1) is a simple contrivance designed to give a more accurate measurement of the time occupied by the contraction and by the relaxation of a muscle than does the mechanism usually employed. It consists of a rectangular piece of metal 7 cm. long and 1½ cm. square placed vertically with a metal rod 15 cm. long and 7 mm. in diameter

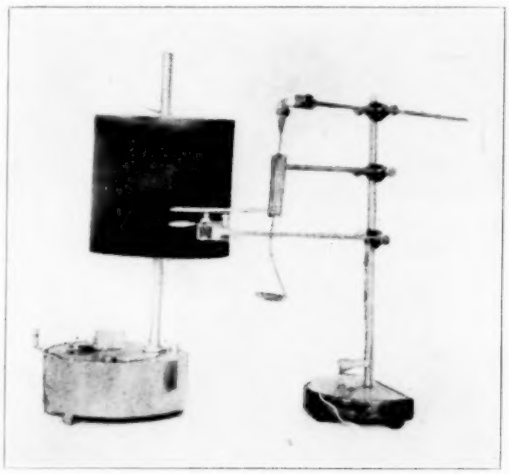

Fig. 1.

attached at right angles near one end to serve as a support. This rod may be clamped to the ordinary stand. Through the center of the vertical block from end to end is drilled a round hole eight millimeters in diameter, and in this a small metal disc, or piston, is accurately fitted. To the upper surface of this disc is fastened a wire for the attachment of the muscle, and to its lower surface is fastened another wire for the suspension of a scale pan. A writing lever is secured to the side of the disc and allowed to project through a slot cut through the cylinder wall from top to bottom. This permits the disc to be moved up and down in its containing cylinder. The muscle may be held in any suitable clamp, in this case a muscle clamp of the type made by the Harvard Apparatus Company.

The muscle lever ordinarily used to record a muscle curve is the radius of a circle and when lifted by the contracting muscle its writing point describes the

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arc of a circle. It is obvious that in making a tracing of a muscle curve on a revolving drum the apex of the curve is moved backward, that is, away from the point at which the curve began, because of two factors; the movement of the surface of the drum past the writing point and the arc drawn by the muscle lever when elevated. The second of these factors adds to the apparent length of the period of contraction an appreciable length of time due entirely to

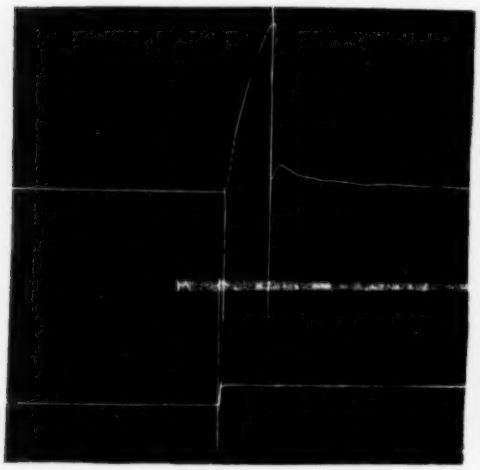

Fig. 2-A.

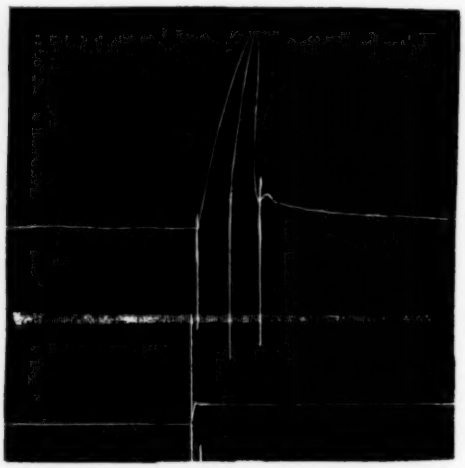

Fig. 2-B.

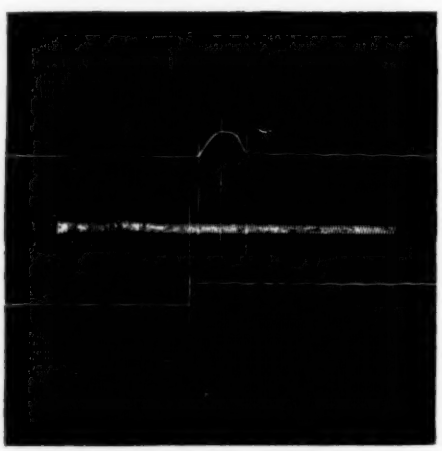

Fig. 3.

the method of operation of the apparatus. In some cases the arc formed by the writing point is so great as to inscribe a muscle curve in which the apex is behind the point where the lever returns to the base line; i. e., the point indicating the termination of the period of relaxation. In such a case the error is obvious, but in every muscle curve drawn by this method there is an error due to the factor described. It is claimed that this error may be eliminated by allowing the writing lever to inscribe its arc from the apex of the

muscle curve to the abscissa line with the drum stationary, and computing the time from the beginning of the curve to the intersection of this arc with the abscissa line as the true period of contraction. The objections to this method are that it is inconvenient, is apt to be inaccurate, and is, therefore, unscientific.

Two muscle curves exemplifying the foregoing statements are shown in Fig. 2. In Fig. 2*A* is seen a muscle curve ruled with vertical lines from the beginning of the curve, the apex, and the point where the lever returns to the base line, to the time record. It is unnecessary to point out the inaccuracy. In Fig. 2*B* a similar curve is corrected by drawing the arc from apex to base line and then ruling the usual vertical lines. This curve still fails to show the proper relationship between time of contraction and time of relaxation.

In Fig. 3 is shown a muscle curve inscribed by our apparatus and ruled

Fig. 4.—One-half actual size.

in the usual manner. In using this device inaccuracies such as may occur by the method just described are impossible. The writing point can move only in a vertical direction and, therefore, the section of the drum that passes the writing point during the contraction and also during the relaxation of the muscle must represent only the time during which the lever was being raised by the contraction of the muscle or allowed to fall by its relaxation. There is, of course, no magnification as with the usual muscle lever, but the ordinary muscle (in this case the gastrocnemius of a frog) with proper adjustment of load and strength of stimulus will give a contraction curve sufficiently high.

The second suggestion that we wish to make is a simple key which can be

Fig. 5.—One-half actual size.

easily made and attached to the Harvard kymograph. It is so constructed that the primary electric current is broken at any one desired point on the circumference of the drum and is always broken at exactly the same point with each succeeding revolution. Our object in making this key was to secure an arrangement that could be made easily and cheaply, so that it would be suitable for use in a teaching laboratory, which would enable the student to obtain a break shock at identically the same point every time the drum revolved. It is unnecessary to point out the advantages of such a device in recording a series of contractions of a voluntary muscle to show the changes in the contraction curve as the muscle becomes fatigued, or in recording the effect of load upon the contraction of such a muscle. It is not suggested that this key is any better than, or even so good as, automatic keys in use in various laboratories; but

it is intended to offer something which may be helpful to those who are using the Harvard kymograph and have felt, as have the authors, the need of some such attachment.

As may be seen from Fig. 4 the apparatus consists of a hard rubber base 4½ cm. long and 2 cm. wide which is attached to the upper surface of the base of the kymograph by two screws passing through the vulcanite block at two corners and entering holes drilled through the metal plate forming the upper surface of the kymograph base. In this hard rubber block two binding posts are fastened for the attachment of wires of the primary circuit. One binding post is shorter than the other and carries a metal bar which can be allowed to rest on the taller binding post and which can be swung upward and backward away from the post on which it rests. To accomplish this it is hinged loosely

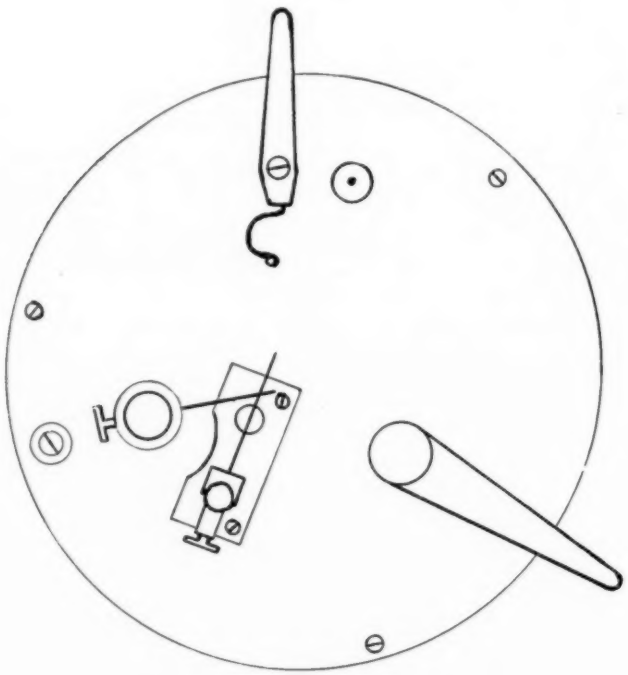

Fig. 6.—One-half actual size.

by a horizontal rod passing through a hole drilled through the shorter of the two posts at right angles to the line joining the binding posts. The only portion of the device remaining to be described consists of a ring (Fig. 5) which encircles the brass sleeve that supports the drum. This ring is held in position by a set screw and carries a rod three centimeters long projecting horizontally. This rod acts as a striker, raises the bridge connecting the two binding posts and carries it onward until it passes beyond the vertical position and drops down and away from the first post. As soon as the bridge is raised the primary circuit is broken and before the drum has completed its revolution ample time is afforded the experimenter to close the short-circuiting key, make the current in the primary circuit by swinging the bridge over into position so as to connect

the two binding posts, and open the short-circuiting key. When this is done the next revolution of the drum gives a break shock at exactly the same point as before. Or, if more convenient, the operator may wait until the curve has been recorded, stop the drum, and reset the key. One great advantage possessed by such a key as we have described is that after the contact has been broken it makes no difference how often the drum revolves there can not possibly be any further stimulation of the preparation until the experimenter closes the key. In our experience this last feature is particularly valuable in the case of students.

Fig. 6 shows the position of the key upon the upper surface of the base of the kymograph.

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## A SIMPLE MOUNTING FOR THE CARBON DIOXIDE APPARATUS OF VAN SLYKE*

By Withrow Morse and L. L. Landenberger, Chicago, Ill.†

THE accompanying figure illustrates a simple method of mounting the apparatus of Van Slyke for carbon dioxide determinations as used in this laboratory.† The larger apparatus is shown here, but the same method is applicable to the microapparatus. The 50 c.c. bulb of the apparatus sits in a clamp‡ (Fig. 2) which has four jaws generously supplied with thick-walled rubber tubing and the bulb is held in place by means of a hook operated by a spiral spring at its base, which draws the hook into firm contact with the bulb. The hook is covered, likewise, with rubber tubing.

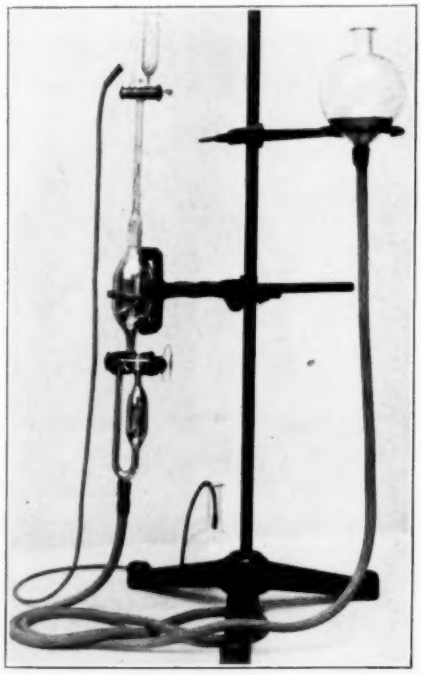

Fig. 1.

The leveling bulb is supported by an ordinary ring fastened to the same ringstand, which is used to hold the apparatus proper. From the sides of the ring, two inches of metal are cut away for the purpose of admitting the leveling bulb.

In the manipulation of the apparatus during a determination, it is necessary to

Fig. 2.

*Van Slyke, D.D.: Jour. Biol. Chem., June, 1917.

†From the Nelson Morris Memorial Institute for Medical Research, Michael Reese Hospital, Chicago.

‡This clamp is patented and made by Wm. Gaertner & Co., 5345 Lake Park Ave., Chicago, and is readily adapted to many other uses in the laboratory.

remove the apparatus from its support. This is simply done by slipping the hook from the bulb. There are no screws necessary.

It is important that the two-way stopcock at the bottom of the 50 c.c. bulb be held firmly in place. This may be done by means of heavy rubber bands, but this obscures the apertures in the stopcock. By means of a piece of wood fitted in a fork around the neck of the stopcock and held firmly against the tube by means of zinc oxide adhesive or a rubber band, displacement of the stopcock and consequent loss of mercury is rendered impossible.

## NOTE ON A UNIFORMLY SATISFACTORY METHOD OF COLLECTING URINE SEPARATELY FROM EACH URETER IN ACUTE EXPERIMENTAL WORK (DOGS)*

By A. B. Luckhardt, Ph.D., M.D., Chicago, Ill.

IT seemed desirable to record briefly a method of collecting urine separately from each ureter which is better than the procedures in common use in acute experiments inasmuch as it is quite satisfactory even in the hands of an amateur.

It will be generally conceded, I believe, that all methods of collecting urine involving cannulas tied in the ureters have this annoying difficulty that the ureter from the start or soon after suffers compression from the abdominal

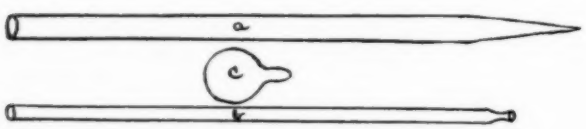


Fig. 1.—(*a*) Steel-tipped brass trocar large enough to admit ureteral cannula (*b*). The wood fiber sphere (*c*) will be found useful in pushing trocar through soft tissues.

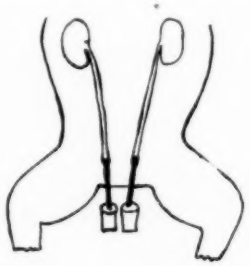

Fig. 2.—Shows the artificial posterior extension of dog's ureters by cannulas introduced into the ureters and held in place by a method described in the text.

wall or surrounding structures or obstruction by a kinking of the ureter at the point of insertion of the cannula, especially when an attempt is made to lead out the collecting cannulas through an incision in the anterior abdominal wall. Particularly is this true if the cannulas are introduced into the ureter near the bladder, the point of election, since insertion near the pelvis of the kidney invites a reflex anuria.

The method I have devised is based on three mechanical physiologic considerations of practical importance: 1. To isolate the ureters through a small abdominal incision just above the symphysis of the pubis. 2. To introduce a

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cannula in such a manner that it will be in line throughout its length with the ureter into which it has been inserted. 3. To maintain the cannula securely in this position throughout the period of experimentation; for everyone knows that very slight pressure on the ureter or kinking of it suffices to stop an otherwise brisk flow of urine.

To accomplish the latter two ends I make use of trocar of brass tubing provided with a very sharp steel tip (Fig. 1*A*) sufficiently large to admit a glass cannula whose tip is blunt (Fig. 1*B*). The trocar is about 15 cm. long with an internal bore of 6-7 mm. The glass cannulas are somewhat longer, the length varying with the size of dog experimented upon. The urinary bladder having been emptied of the contained urine and fecal masses removed through the anus by manual compression, through a laparotomy incision just above the symphysis two small skin incisions are made, each one medial to the tuberosity of the ischium. A wood-fiber sphere having a small projection which fits snugly in the open end of the brass trocar (Fig. 1*C*) is attached to the latter. The trocar is grasped firmly in one hand with the wood-fiber plug in the center of the palm; the tip of the trocar is inserted into one of the skin incisions near the tuberosity of the ischium and then pushed through the perineum and pelvis under the symphysis on the pubis so that the trocar, when its tip appears above the brim of the true pelvis lies in a direct line with the ureter. The wood-fiber sphere is disengaged from the trocar. A ureteral cannula (Fig. 1*B*) is pushed up into the trocar (tip first) as far as it will go. The trocar is removed by pulling it out of the abdominal incision leaving in its place the ureteral cannula in exact line with the ureter. The cannula is tied into the ureter in the usual way. In short, the ureter is artificially extended backwards and to the exterior by a cannula which lies *in line* with the ureter and is held there firmly by the tissues surrounding it. (Fig. 2.)

In plunging the trocar through the tissues it is, of course, essential that the tip be directed properly so that it will subsequently lie in the proper position. The index finger of the other hand will be found useful as a guide.

If the introduction of the long cannula into the ureter is found too difficult, a small cannula may be inserted into the ureter, a longer piece of glass tubing brought in apposition with it by means of the trocar, and the two then joined by a piece of thick-walled rubber tubing.

After the cannulas are in place they are freed from air by displacing the latter with physiologic salt solution or water contained in a bent Pasteur pipette inserted high up into the neck of the ureteral cannulas.

For convenience in introducing the trocars and in collecting urine it is desirable to raise the dog's pelvis from the animal board by a two-inch wooden block.

Since the ureters converge towards the bladder, it would possibly be still better to push the trocar from the left skin incision to the right brim of the true pelvis and from the right skin incision to the left brim of the pelvis. The ureteral cannulas when inserted would then cross in the median line under the symphysis. But I have not found it necessary to cross the cannulas to conform with this strictly theoretical requirement.

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## EDITORIALS

### *An Explosive Epidemic of Influenzal Disease at Fort Oglethorpe*

MAJOR SOPER makes a report upon the above-named epidemic of which the following is an abstract:

A disease strongly resembling influenza became prevalent in the Oglethorpe camps about March 18, 1918. It soon assumed pandemic proportions. Within two weeks every organization in Camp Forrest and the Reserve Officers' Training Camp was affected. It seems to have visited only a part of Camp Greenleaf. The War Prison barracks were not invaded. After about three weeks the epidemic subsided rapidly. The number of cases sent to hospital or to quarters was 1,468 in a total strength of 28,586. Owing to the fact that many cases were not severe, the total number of officers and men attended can not be given; an estimate based on replies to a circular letter of inquiry to the several organizations of the study of the records of the hospitals indicates that not less than 2,900 cases have occurred in Chickamauga Park.

The attention of the Camp Surgeon's Office was called to the existence of this disease on March 18, at which time the writer saw a number of men appear at sick call in the 51st Infantry, suffering with the disease which the regimental surgeons were unable to diagnose. The symptoms were as follows: Headache, pain in the bones and muscles, especially the muscles of the back, marked pros-

tration, fever (sometimes as high as 104°). Sometimes there was conjunctivitis, coryza, a rash and possibly nausea, recovery taking place in a few days.

In most cases a definite diagnosis was not made at the regimental sick call, but at the receiving ward, when a name was given, it was usually called influenza.

On April 3 it was recommended that steps be taken to ascertain from the several organizations under the supervision of the camp surgeon from other camps in the Oglethorpe region, the essential facts concerning the nature and epidemiological progress of the disease. A circular letter of inquiry upon these lines was sent out on April 4 to all organizations. Replies to this questionnaire indicated that the disease was first noticed in epidemic form on March 18 in the 51st Infantry. In some organizations all cases were sent to hospital; in others their cases were treated in quarters or in the regimental infirmary. This does not mean that the disease was more severe in some organizations than in others. Difference in the disposition of the sick depended not so much upon the severity of the case as upon the local facilities for dealing with them. Records show that there were twice as many patients dealt with in quarters as in hospitals and there were probably twice as many cases existing as were carried on sick report.

The replies were unanimous in stating that the disease was not restricted to recruits, nor to men who had already experienced or failed to experience an attack of measles, German measles or scarlet fever. One attack did not protect against another.

In all the organizations the epidemic was first located in companies before it became general. In many instances a large proportion of the men were affected. According to the registrar of the Base Hospital, fully one-half of the total number of patients in the hospital had the disease. The rate at which the epidemic progressed made it impossible to trace its path, if indeed it followed any.

The incubation period was short, usually not over one or two days. Instances were found in which men isolated in quarantine were attacked apparently through contact with those who brought them food or approached them for other reasons. At the Post Hospital a number of surgical cases in tents were infected, apparently by an orderly. In Co. B, of the 15th Machine Gun Battalion, which was in quarantine on account of scarlet fever, nearly every one present was attacked. In Company A, 52nd Infantry, a company which was quarantined, the men appeared to be protected by reason of their isolation.

Some organizations suffered more than others for no apparent reason. The 52nd Infantry had the most and the 54th Infantry the fewest cases. In the 52nd Infantry and the 15th Machine Gun Battalion, one in every seven of the officers and men was on sick report. In one ambulance company the proportion was one to six, while in others it ran as low as one to twenty-two.

Upon the recommendation of Major Soper, a board was created on April 3 to determine the nature of the disease causing the unusually large number of admissions to the Post Hospital with the diagnosis, "fever, type undetermined," "influenza," etc. This board has not yet finished its work. The appearance of the epidemic in various organizations of the 6th Division was so nearly simultaneous as to suggest that a common cause was operating or that the disease was

spreading with great rapidity. The first recorded notice of the disease was in the 51st Infantry on March 18. Three days later it was recognized in the 52nd Infantry and the 15th Machine Gun Battalion. On March 25, the 16th, 17th, 18th, and 19th Machine Gun Battalions encountered it. The 11th Infantry was infected on March 26, and the Camp Quartermaster's Office on March 28; the 11th Cavalry on March 30, and the 53rd and 54th Infantry on April 1. Camp Warden McLean seems not to have been visited by the epidemic until April 7; by the 9th, 200 cases of more or less severity had occurred there.

The possibility that the disease which has just become epidemic has long existed in these camps in sporadic form, but has not hitherto attracted notice because of its infrequence, has received careful consideration. At first there seemed much to recommend this theory. Clinicians on the hospital staff claimed to have seen the disease at times since the summer of 1917. They say that it became rather prevalent in September. It is believed by some that the germ of influenza, like that of some other diseases, is constantly present in every large community; that it is not always virulent, but under certain conditions it acquires increased virulency.

If the organism which has caused the present epidemic has long been in existence in the Oglethorpe camps, it is not apparent why it has suddenly become so active. It would seem that the conditions for its epidemic prevalence have existed for a long time. Recent weather conditions, uncomfortable as they have been, have not been so disagreeable as they were in January. The theory that the explosion is of local origin needs a better explanation than can apparently be given it.

Studies by Major Soper have been made to ascertain whether the state of the weather was in any way accountable for this epidemic. This inquiry covers the period from March 1 to April 13, approximately three weeks before the epidemic began and more than three weeks later; 44 days in all. For the six weeks' period there was less than half the amount of sunshine which was possible. On 11 days there was 1/5 or less of sunshine which would have occurred had the days been perfectly clear. On 9 days the sun was obscured during 90 per cent of the time. The mornings, evenings and nights were misty; the day was generally well advanced before the sun appeared. The days were fairly mild, but nights and mornings were damp and chilly. The highest temperature on any day was 82. It was warmer than 75 degrees seven times; over 65 degrees twenty-five times, and over 55 degrees thirty-eight times, or nearly every day. The mean daily temperature was always under 75 degrees or less, about as often as it was higher than that figure. The minimum daily temperature was 45 degrees, or less, half the time. On 11 days the mercury fell to 40 or under. These temperatures would not have been in the least uncomfortable had the weather been less humid. There was a sudden drop in temperature on the 9th of March. On the evening of that day the thermometer fell from 68 degrees at 7:00 P.M. to 38.8 at 7:00 A.M., or 30 degrees over night. The fall was followed by a rise to 76 degrees and then by a drop of 14 degrees to 62. On March 14, the temperature fell from 71 to 60 in ten minutes. Another fall of 9 degrees, this time of from 72 to 63, occurred on the morning of April 3.

The relative humidity in the morning at 7:00 o'clock was nearly 60 per cent or over. For nearly three-fourths of the time it was 70 or more. On 18

out of the 44 days the humidity reached 80 or more in the morning. The humidity was somewhat less in the evening. It was 70 per cent or more about one-fourth of the time. About one-third of the time it was 60 or more. At noon a humidity of 60 per cent occurred nearly one-half the time, 70 per cent over one-third of the time and 80 per cent about one-fifth of the time. These humidities were not remarkable in themselves. Considered in connection with the temperature they were of a sort to aggravate respiratory affections.

The weather was cloudy, damp and chilly. It was not cold nor wet, but the nights and especially the mornings were decidedly damp and uncomfortable. The difference between the air indoors and out was marked. Drafts were particularly noticeable.

Reviewing these facts about the weather, it can not be said with certainty that the conditions of temperature and humidity have had much to do with the epidemic, nor can it be denied that they played an important part in predisposing the troops to attack. Obviously the weather conditions have led the men to gather indoors where they have been especially exposed to infection from one another, and it has had a chilling effect which is an important factor in the progress of all respiratory infections.

An inquiry was made to ascertain whether the troops were exposed to an unusual extent to the weather, to excessive fatigue, or in any other way before or after the epidemic started. This line of investigation brought no suggestive information to light.

No exceptional prevalence of influenza or other similar infectious disease has existed in Chattanooga or in the extra cantonment zone. An effort was made to shed light on the identity of the disease by studying the record of other cases of sickness which had been sent to the hospital under the designations of "fever, type undetermined" and "influenza" during the six months preceding the epidemic. These designations have never been definite; they have seldom been based on conclusive evidence at the hospital. Bacteriological examinations have seldom proved the influenza bacillus to be the causative agent of the cases called "influenza." From time to time this bacillus had been found in the secretions of the nose and throat of troops, but has not been proved to be the cause in any large amount of sickness. "Fever, type undetermined" and "influenza" have been merely convenient expressions by which to designate cases of an indetermine sort which demanded treatment and had to be called something.

Of a series of 161 cases of "fever, type undetermined" sent to the hospital before the present epidemic broke out, 59 turned out to be bronchitis and 41 pneumonia; 61 were called "influenza." In some instances "fever, type undetermined" has been found to be measles, scarlet fever, otitis media and meningitis. Out of 189 cases diagnosed "influenza" at the regiments, 150 turned out at the hospital to be some other disease.

It is probable that the epidemic disease was recently brought to these camps. If it is genuine influenza, and the epidemiological features no less than the leading symptoms seem to point to that disease, there is here offered the most reasonable explanation of the outbreak which is now possible. No other disease spreads so fast or is so prostrating, considering its symptoms. Influenza may be nearly explosive in character, it spreads as rapidly as personal

communication permits. Personal contact is intimate in the Oglethorpe camps, especially between men in companies and regiments. To some extent the regiments keep separate, but there is a general mixing at places of amusement in camp and Chattanooga. It is worthy of remark that the regular Officers' Training Camp is an organization which mingles but little with others in the Oglethorpe camps, and that here the epidemic was late in appearance. The same may be said of a part of Camp Greenleaf. The War Prison Camp is entirely separate and escaped infection. The epidemic seems to have burned out for want of suitable material, probably with the gradual but rapid decrease in virulence.

Reviewing the whole subject, it may be said that an epidemic of influenzal disease became prevalent in the Oglethorpe camps toward the latter part of March, 1918. The identity of the disease has not been positively determined after nearly a month of observation. It may have been an outburst of a form of sickness which has long existed in sporadic form in these camps. It may have been brought to the camps from outside. The weight of evidence is in favor of the latter theory. Such laboratory evidences as may be available upon this point will be reserved for the initial report of the board which was created on April 3 in order to determine the identity of the disease.

It is a highly infectious disease with a short period of incubation. The weather has encouraged the epidemic, but is not apparently responsible. The disease is respiratory in type, with a strong resemblance to influenza in some of its most characteristic symptoms, as note the fever, pain in the back and legs and great prostration.

The cause of the rapid spread undoubtedly lies in the great infectivity of the causative agent, its short period of incubation and the intermingling of the troops. One thing seems clear, the disease could never spread unless the buccal or nasal discharge of the sick got into the mouths or noses of susceptible persons. The nature of the epidemic seems to show the extent to which this interchange takes place under the conditions which surround these troops.

—*V. C. V.*

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## *Epidemic Meningitis and Its Treatment*

THE belief that epidemic cerebrospinal meningitis is essentially a primary infection of the meninges has been generally accepted despite the very obvious clinical symptoms which would seem to point in a different direction, and despite the fact that a consideration of the route by which the organisms must follow in order to reach the meninges would seem to suggest the probability that the blood stream would be primarily involved. When symptomatology and pathogenesis are taken together the logic is entirely in favor of the primarily septic nature of the disease.

It is just as Herrick[1] says,—"the meningeal aspect of meningococcus infection has usurped such a prominent place in the commonly accepted ideas of the nature of epidemic cerebrospinal meningitis, that important facts have been kept in the background. The very name of the disease and of the causative

organism have given undue prominence to a single manifestation of the condition." The conception that meningococcus infections are primarily septic conditions and that the meningitis is a secondary affair has been expressed, but, as Herrick says, it has never been adopted as a working basis for early diagnosis and treatment. This is true to such a degree that the premeningitic stage of the disease,—the period of the disease prior to the time when localization occurs,—has been practically disregarded. It is upon this stage of the disease and upon treatment during it that Herrick dwells in his account of his experience with 208 cases at Camp Jackson.

The facilities for the study of these cases at Camp Jackson, while rudimentary in the extreme in some respects, were in other ways ideal. It was realized by the Division Surgeon that good results would depend upon early diagnosis and treatment, and therefore he instructed the regimental surgeons to refer at once to the Base Hospital all men complaining of headache, fever, vomiting, or other suggestive symptoms. Such a system would insure not only getting the cases of meningitis at an early stage, but would also make it possible to catch cases of other infections. The result of this order was that a very unusual number of early cases of meningitis were made available for study.

The major results of the study are summarized as follows: The earliest stage of the disease is brief and lasts on an average about 48 hours, during which the symptoms are those of a generalized infection. In some cases this is the only stage and the disease is of the abortive type, or, in exceptional instances of the fulminating type without meningeal symptoms. One-half of Herrick's cases were recognized in this "premeningitic period." In a very large proportion of the cases there was an associated upper respiratory tract disturbance, a phenomenon of such frequent occurrence that, as Herrick, Medlar,[2] Mink,[3] and Thomsen and Wolff[4] have suggested, it is no mere coincidence. Of the early symptoms the skin manifestations are most important. The predominant skin sign is a petechial rash which appears about the shoulder or pelvic girdle if at all, and next in frequency, over the trunk, extremities, face, oral, mucosa and conjunctiva. It appears with astonishing rapidity in crops and in some of the severe cases the patient becomes well dotted within an hour. In the presence such a rapidly developing hemorrhagic rash is diagnostic. Purpura is a feature of fulminating cases.

Next to the rash the most important symptoms are modifications of the reflexes, especially *unequal* enhancement of the deep reflexes. Also slight chills are present and headache is present in 85 per cent of the cases. In the presence of a combination of any two of these suspicious symptoms a lumbar puncture is done and the fluid, even if it is clear, comes out under slight increase of pressure and may show a normal cell count. Long centrifugation followed by careful examination of the sediment will usually reveal a few pairs of the cocci. If examination of the fluid first obtained is not productive, a second puncture is made shortly after it, and in this the organisms will be found. At this very early stage of the disease Baeslack[5] and his associates have found meningococci in the blood stream in 36 per cent of the cases examined.

Herrick describes four types of meningococcic sepsis, as follows:

The abortive type. A mild, systemic disturbance without a local focus of

suppuration. In this the diagnosis depends upon a demonstration of the organisms in the spinal fluid, blood, nasopharynx, or conjunctiva. The importance of cases of this type is chiefly epidemiologic because they are a menace to susceptible contacts.

The ordinary type. In this the symptoms of meningitis develop gradually, unconsciousness is rare, and the course may be prolonged. The chief emphasis is upon the meninges. Hydrocephalus is a danger and the response to intravenous serum therapy is often less prompt than in the more severe cases.

The severe type. In this there are all the evidences of a severe toxemia. The petechial rash appears with great rapidity. Death may occur before metastasis takes place. The response to serum therapy by the intravenous method is, as a rule, prompt. Intraspinous serum treatment alone is usually insufficient. Diagnosis in the premeningitic stage is usually possible, and blood cultures are usually positive.

The fulminating type. In this as a rule meningitis is not present. Purpura is characteristic. Death is usually exceedingly prompt, and serum treatment is commonly ineffective.

Herrick has worked out the following method of procedure as the result of his study of 208 cases: On admission a patient presenting any combination of the very early symptoms is immediately subjected to lumbar puncture. If the fluid is cloudy enough it is removed to reduce the intraspinous pressure to an approximate normal and a less amount of serum is at once allowed to run into the spinal canal. If the fluid is clear no intraspinal injection is made. The fluid is rushed to the laboratory in a thermos container and immediately examined. In the meantime the patient receives a desensitizing dose of serum. One hour later 50-120 c.c. of serum are given by vein, the first 15 c.c. at the rate of 1 c.c. per minute. In cases of ordinary severity this dose is repeated every twelve hours until the temperature becomes normal or until six to eight doses have been given. In severe cases serum is repeated every eight hours until the desired results are produced. For further details the original article should be consulted.

The results of this procedure in treatment are that the total mortality in the 208 cases was 26 per cent. In 129 cases treated by intraspinal methods alone or with but small doses by the veins, the mortality was 31.7 per cent. In 79 cases treated with the larger doses of serum by the intravenous method and with average doses intraspinally the mortality was 16.4 per cent. The mild cases do well with either method. In the severe cases the intravenous method was especially brilliant. Intravenous therapy had the additional value over the older methods in that it reduced complications. Thirty-one per cent of the cases treated by the older method developed complications. In the group receiving the larger intravenous doses the percentage of complications was fourteen.

—*P. G. W.*

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## *Epidemic Bronchitis at Fort Oglethorpe, Georgia*

MAJOR GEORGE A. SOPER, S. C., N. A., has made a report upon epidemic bronchitis at Fort Oglethorpe. The following is an abstract of the same:

Bronchitis has been well-nigh universal in the Oglethorpe group of camps. Within ten days after their arrival newcomers have generally been attacked, the symptoms often being pronounced from the start. Sneezing and coughing are early signs. In the barracks, mess halls, lecture rooms and places of amusement, during November, December and January there was seldom a moment when coughing was not noticeable and continuous. It is estimated that 80 per cent of all the troops were affected. The epidemic abated in February with the advent of warm weather. Laboratory findings do not agree that any single organism has been the cause. Streptococci, staphylococci, influenza bacilli and other organisms found in the noses and throats of healthy people and sometimes associated with disease have been isolated, but not under circumstances which have led to any of these germs being demonstrated as the microbic cause of the bronchitis. The infectious matter has passed from person to person, probably in three ways: First, men have talked with one another at close range, permitting mouth germs to be projected directly into one another's faces. In the second place, there has been a general impregnation of the atmosphere in confined spaces. In the third place, articles handled by the infected have been transmitted to others. In these ways the amount of infectious matter which has passed from person to person must have been large and with lowered resistance, the infection has rapidly spread.

Predisposing and contributing causes existed to some extent. The weather was unfavorable. Changes in the temperature were frequent and marked. The ground was cold, the air damp and the nights cold. Often men did not have dry shoes for weeks at a time. Some spent the entire winter in khaki. The men themselves were ignorant of simple personal precautions which might greatly have lessened their chances of infection. All of the severe cases have gone to the hospital. The universal prevalence is significant both on its own account, and because of the light which it throws upon the spread of other respiratory diseases in these camps. Although most persons regard bronchitis with comparative indifference, it is a disease of much significance. It is the common saying among the troops that the "bronchial cold" which attacks them soon after their arrival remains with them as long as they stay in camp. Its characteristic hard, explosive cough remains after other symptoms have disappeared. For the time it often unfits a man for duty and there are few sufferers whose efficiency has not been impaired by it. The bronchial pneumonias of these camps have been frequent sequelæ to bronchitis. Whether bronchitis renders a man especially susceptible to other acute respiratory diseases is a question of much interest. Like pneumonia one attack does not protect against others, but on the contrary seems to predispose its victim to subsequent attacks. It is not at all probable that bronchitis increases resistance to measles, scarlet fever, pneumonia and other such diseases. The part which bronchitis may play in the spread of other respiratory infections gives reason for regarding it as a camp disease of the utmost importance. A carrier of meningitis may be relatively harmless so

long as he is in good health, for then the germs which he harbors are fairly well locked up in his nose and in his throat, but when he experiences an attack of bronchitis he sneezes and coughs and at each paroxysm germs are shot into the air. Therefore, it is reasonable to suppose that measles, scarlet fever and other respiratory diseases have been spread by bronchitic soldiers. It may be asked if the exchange of bacteria from the nasal pharynx is so general, why is it that more sickness has not occurred. The answer probably is that most robust soldiers possess a fair degree of immunity acquired either by one attack as in the case of measles, or by frequent exposure without suffering from the disease.

The bronchitis which has prevailed in these camps may be designated as an acute infectious inflammation affecting in rapid succession downward the nasopharynx, the larynx, trachea, and first and second divisions of the bronchial mucosa. The symptoms are coryza, chilly sensations, hoarseness and soreness of throat, weakness, muscular soreness and slight fever (100 to 101°). In severe cases the temperature may rise to 103° with a correspondingly rapid pulse, accompanied by substernal soreness and tightness of the chest. At first the cough is dry and unproductive. It frequently occurs in paroxysms causing muscular pain and soreness along the costal margin at the attachment of the diaphragm. On the third or fourth day, as a rule, the cough loosens and expectoration appears. At first it is scanty and mucous, later it is abundant and mucopurulent. Only negative results are obtained on palpation and percussion. On auscultation sibilant rales may be noted, except when resolution begins, when fine and coarse mucous rales are to be heard. The breath sounds are harsh. Bronchitis may be associated with other diseases such as measles, mumps or scarlet fever. When not complicated, recovery occurs at best within a week, although a chronic form may supervene and continue for months.

Although chronic bronchitis as seen in the quarantine camps is believed to be a definite entity, it is not always so diagnosed. Cough, elevation of temperature and muscular soreness accompany acute nasopharyngitis and tracheolaryngitis as frequently as bronchitis. A positive diagnosis of bronchitis is impossible unless harshness of breath sounds, sibilant and sonorous rales are audible, or in a stage of resolution, fine and coarse mucous rales are heard. Many cases are diagnosed as bronchitis from the symptoms alone.

Pneumonia is not frequently preceded by acute bronchitis, and acute bronchitis rarely terminates in pneumonia except when it accompanies measles. In measles there may be an extension to the terminal bronchi, and the intercommunicating air cells, under which circumstances bronchopneumonia develops.

It is claimed by some that acute bronchitis can frequently be arrested in its early stages by the local application of silver nitrate, 40 grams to the ounce. This solution is applied to the tonsils and erythematous areas in the pharynx. Nasopharyngeal treatment by sprays is also useful by limiting the source of supply of infectious material which is generated in the nasopharynx.

—*V. C. V.*

## *Procaine and Novocaine Identical*

TO THE EDITOR:

It appears that in certain quarters the attitude is taken that the local anesthetic sold as Procaine is not identical with that marketed as Novocaine. The Subcommittee on Synthetic Drugs of the National Research Council believes it important that this misunderstanding should be corrected and hence offers the following explanation:

The monohydrochloride of para-amino-benzoyldiethylamino-ethanol, which was formerly made in Germany by the Farbwerke, vorm. Meister, Lucius and Bruening, Hoechst A.M., and sold under the trademarked name Novocaine, is now manufactured in the United States. Under the provisions of the Trading with the Enemy Act, the Federal Trade Commission has taken over the patent that gave monopoly for the manufacture and sale of the local anesthetic to the German corporation, and has issued licenses to American concerns for the manufacture of the product. This license makes it a condition that the product first introduced under the proprietary name "Novocaine" shall be called Procaine, and that it shall in every way be the same as the article formerly obtained from Germany. To insure this identity with the German Novocaine, the Federal Trade Commission has submitted the product of each firm licensed to the American Medical Association Chemical Laboratory to establish its chemical identity and purity, and to the Cornell pharmacologist, Dr. R. A. Hatcher, to determine that it was not unduly toxic.

So far, the following firms have been licensed to manufacture and sell Procaine:

The Abbott Laboratories, Ravenswood, Chicago.
Farbwerke-Hoechst Company, New York, N. Y.
Rector Chemical Co., Inc., New York, N. Y.
Calco Chemical Company, Bound Brook, N. J.

Of these, the first three firms are offering their products for sale at this time, and have secured their admission to New and Nonofficial Remedies as brands of Procaine which comply with the New and Nonofficial Remedies standards.

While all firms are required to sell their product under the official name "Procaine," the Farbwerke-Hoechst Company is permitted to use the trade designation "Novocaine" in addition, since it holds the right to this designation by virtue of trademark registration.

In conclusion: Procaine is identical with the substance first introduced as Novocaine. In the interest of rational nomenclature, the first term should be used in prescriptions and scientific contributions. If it is deemed necessary to designate the product of a particular firm, this may be done by writing Procaine-Abbott, Procaine,-Rector, or Procaine-Farbwerke (or Procaine [Novocaine brand]).

Julius Stieglitz, Chairman,
Subcommittee on Synthetic Drugs, National Research Council.

EDITOR'S NOTE:

The Federal Trade Commission recommends the use of the official name of the licensed drugs in connection with all written articles and advertisements, and

if the proprietary brand name is to be used, to place this side by side with the official name.

The official names so far adopted by the Federal Trade Commission are:

*Arsphenamine* for the drug marketed as Salvarsan, Diarsenol, and Arsenobenzol, etc.

*Neoarsphenamine* for the drug marketed as Neosalvarsan, Neodiarsenol and Novarsenobenzol, etc.

*Barbital* for the drug marketed as Veronal.

*Barbital-Sodium* for the drug marketed as Medinal and Veronal-Sodium.

*Procaine* for the drug marketed as Novocaine.

*Procaine Nitrate* for the drug marketed as Novocaine Nitrate.

*Phenylcinchoninic Acid* for the drug marketed as Atophan.